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DIAGNOSIS OF ERYTHROBLASTOSIS (HEMOLYTIC ANEMIA) IN THE MACERATED FETUS

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ON postmortem examination of a macerated fetus it is often difficult to determine whether erythroblastosis is present, and definite criteria for such a diagnosis have never been established. At the present time there is a widespread tendency to regard as having this disease all macerated fetuses from mothers whose red blood cells are shown not to contain Rh, the fact being overlooked that intrauterine death may occur in fetuses of such women from the same causes as function in women whose red cells contain Rh.

Among all infants who die before birth or in the first few days of life those who die before the onset of labor make up the majority of the group in whom a diagnosis as to the cause of death cannot be made from the necropsy or the clinical history. In a previously reported series of 2,000 infants who died in utero or during the neonatal period and on whom autopsies were performed,[1] those who died before the onset of labor in whom no cause of death could be ascertained made up 19 per cent. In 57 per cent of the antenatal deaths a cause could not be found. Rh determinations were not done on the mothers of these infants, but subsequent studies[2] have shown that among women who give birth to macerated fetuses in which death is due to causes other than erythroblastosis, the incidence of those whose erythrocytes do not contain an Rh factor is approximately the same as that among women in the general population.

The prognosis for future successful pregnancies is poor if a woman once bears an infant who dies of erythroblastosis. It is therefore extremely important to arrive at an accurate diagnosis. No woman should be urged to forego further pregnancies unless some definite evidence of the disease exists in the fetus in question.

Macerated fetuses in relation to this problem may be divided into three groups:

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1. Potter, E. L.: J. A. M. A. **115**:996, 1940.
2. Unpublished data.

1. Late premature or term fetuses in which maceration is slight. In these the same criteria which apply to nonmacerated fetuses and infants may be used.

II. Abortions: previable or very premature fetuses. These almost never show a pathologic condition which can be diagnosed as erythroblastosis. If a woman has previously given birth to an infant with erythroblastosis, it is probably justifiable to believe that the same cause operated in causing the subsequent early intrauterine death. There is no positive proof, however, that this assumption is true. Abortion or early fetal death in women pregnant for the first time or in women who have never succeeded in carrying a child to term (the so-called habitual aborter) is almost never due to erythroblastosis.

III. Late premature or term fetuses with marked maceration. It is this group of infants with which this paper is particularly concerned, and it is believed that if careful postmortem studies are made, the presence or the absence of erythroblastosis can usually be established. Of especial importance is the presence of: edema, especially of the face; mild macroglossia; hypertrophy of the spleen and the liver; normal zone of growth at the ends of the long bones; enlargement of the placenta; erythroblastemia in placental vessels; basophilic erythroblasts in pulmonary capillaries; absence of Rh in the mother's erythrocytes and presence of Rh in the father's erythrocytes.

Even if the degenerative changes are advanced, erythroblastosis usually can be easily diagnosed in the typical case. All of the findings just listed will be present. Anasarca is frequently extreme and is often so severe that the abdominal wall is 1 to 2 cm. thick as a result of separation of the muscle layers by the edema of the intervening connective tissue. The tongue is edematous, and the tip protrudes through the separated lips (fig. 1 *A*). Pleural or peritoneal effusions may be present and, if large in amount, may compress the viscera against the posterior wall of the body. The organs of a macerated fetus weigh less than those of a nonmacerated fetus of similar size, but in spite of this the weight of the spleen is usually considerably increased (fig. 1 *B*). The liver is also frequently enlarged but not as markedly or as constantly as the spleen. The thymus is usually hypoplastic. The heart may be of normal size or slightly enlarged. At the ends of the long bones the zone of growth is normal.

The placenta is often greatly enlarged. At term the average placental weight without cord or membranes is about one-seventh that of the fetus. In erythroblastosis, it is frequently one-fourth as heavy as the fetus, and at times it may exceed half of the fetal weight. The enlargement is due to actual increase in the size of the individual villi brought about partly by edema and partly by tissue increase. Fluid

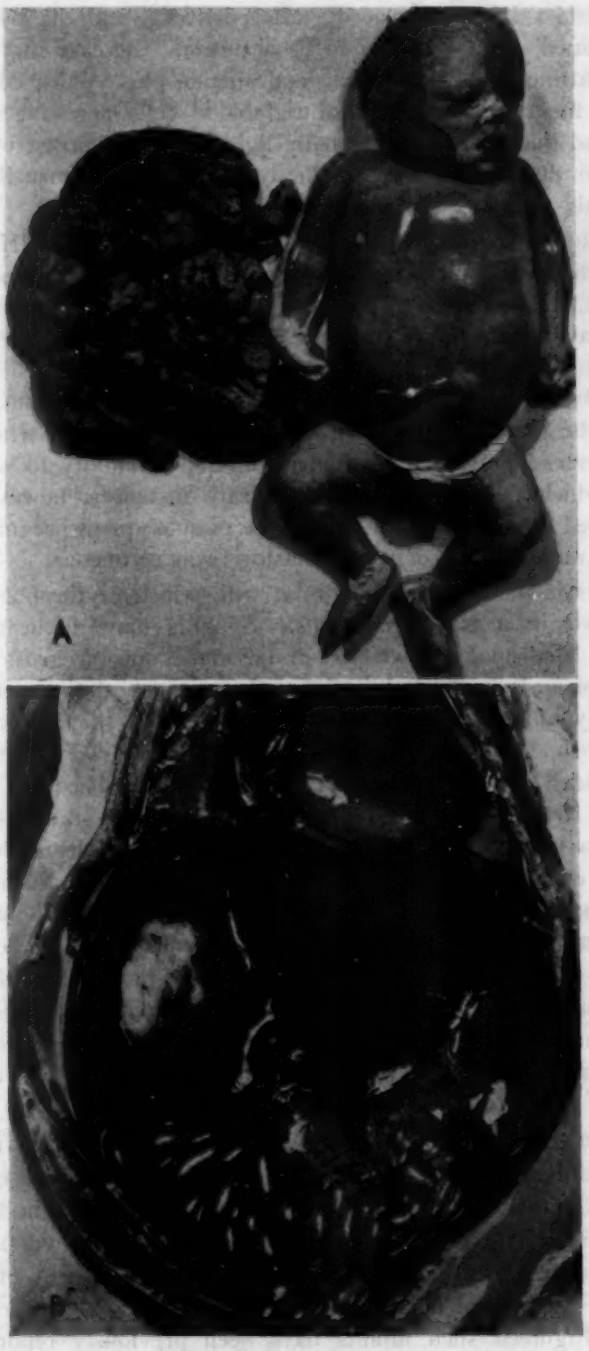

Fig. 1.—*A*, erythroblastosis in a macerated fetus and placenta. *B*, enlargement of the spleen and the liver of a fetus with erythroblastosis.

rapidly exudes from the placenta after delivery, and the weight must be determined at once if it is to be accurate. Increase in villous size produces a thick bulky placenta; fetal anemia plus villous edema gives less than the normal number of red blood cells per unit volume of placenta, so that the color is usually light pink in contrast to the dark red of the normal placenta. The cotyledons are unusually sharply demarcated.

The mother's erythrocytes are usually free of Rh. If they are not, the diagnosis must be regarded with suspicion no matter how typical the findings seem to be. Infrequently some other antigen, such as Hr, may be responsible for the manifestations of erythroblastosis, and a few cases have been described which were presumed to be due to A or B immunization. It is also possible for one of the subgroups of Rh to be responsible for sensitization, and a woman whose erythrocytes possess one Rh fraction may develop immunity to some other fraction which they lack. Except in rare instances, however, if the mother's red cells contain Rh, the course of subsequent pregnancies will show that the diagnosis of erythroblastosis was erroneous.

Syphilis is the principal condition with which erythroblastosis may be confused in a macerated fetus. Syphilis may duplicate any or all of the abnormalities which can be made out on gross anatomic examination. If sufficiently advanced to cause the aforementioned changes, syphilis, in addition, usually produces a thickened, irregular epiphyseal line at the ends of the long bones. The author has observed such a change in association with erythroblastosis of a non-macerated fetus in 2 cases in which histologic study, stains for Treponoma pallidum and thorough investigation of the mother, father and other children failed to show evidence of syphilis. Such a change in the long bones is therefore not conclusive evidence of syphilis but its occurrence in any other condition is extremely rare. The presence of syphilis can usually be corroborated by the presence of the disease in the mother, the demonstration of T. pallidum in the tissues and the presence of histologic changes which differentiate the condition from erythroblastosis. It is also possible to have the two conditions coincident in the same fetus.

Another condition of extreme hydrosis occurs in the fetus that must be differentiated from erythroblastosis. It is associated with extreme anasarca, with pleural and peritoneal effusions and at times with placental hypertrophy, but the spleen is usually hypoplastic, the mother's red cells are usually free of Rh, and subsequent pregnancies end in the delivery of normal infants. Malformations are occasionally present. Eighteen such infants have been previously reported,[3] and

3. Potter, E. L.: Am. J. Obst. & Gynec. **46**:130, 1943.

2 more have been subsequently observed. Nothing is known of the etiologic factors of this condition.

In contrast to the fetuses with typical erythroblastosis here described are those which have the disease in spite of showing little gross evidence that it is present. Not infrequently such fetuses appear normal on the cursory examination macerated fetuses are apt to receive. There may be little edema, and what is present may be mistaken for a change due primarily to maceration. Careful examination, however, usually reveals definite edema of the face, especially of the eyelids, even if it is otherwise absent. Protrusion of the tongue between slightly separated lips is common.

The internal viscera may reveal nothing abnormal, although in most instances some enlargement of the spleen will be observed. If the fetus has been dead for several weeks prior to delivery, even though the measurements may be abnormally great, the weight may be so reduced that it is within normal limits.

In such fetuses, histologic examination of the liver, the spleen, the kidneys and other organs, which is ordinarily so important in arriving at a diagnosis, is impossible. The rapid degeneration of the abdominal organs that occurs after death causes complete loss of cellular detail within a few days. Henderson [4] reported that he could demonstrate an increase in intralobular connective tissue in the liver in the majority of macerated fetuses with erythroblastosis. In my experience this increase is occasionally present (as it is also in nonmacerated fetuses and infants with erythroblastosis) but is not sufficiently constant or distinctive to be of much value. It is also frequently found in syphilis.

One organ, however, which is of great value even when extreme maceration is present is the lung. This tissue retains its affinity for dyes long after all other viscera have lost theirs, and some histologic details can be made out when the fetus is delivered even weeks after death has occurred. Of especial importance is the fact that erythroblasts and normoblasts are among the last cells to lose their affinity for stains (fig. 2*A*).

An interest in the contents of the pulmonary alveoli of macerated fetuses originally led to routine sectioning in this laboratory of all lungs regardless of the degree of maceration. It soon became evident that erythroblastosis which was previously unsuspected could be occasionally diagnosed from sections of lung. Examination of the lungs of over a thousand macerated infants has failed to reveal in any other condition the findings about to be described.

In the lungs of both macerated and nonmacerated fetuses an interesting picture presents itself. Local erythropoiesis almost never occurs.

4. Henderson, J. L.: Arch. Dis. Childhood **17**:49, 1942.

Even in the interstitial tissue around the blood vessels, where in comparable places in other organs erythropoiesis may be marked, there is little or no evidence of blood cell formation. Within the capillaries of the alveolar walls, however, there are large numbers of the most immature forms of red blood cells, cells which in blood smears are

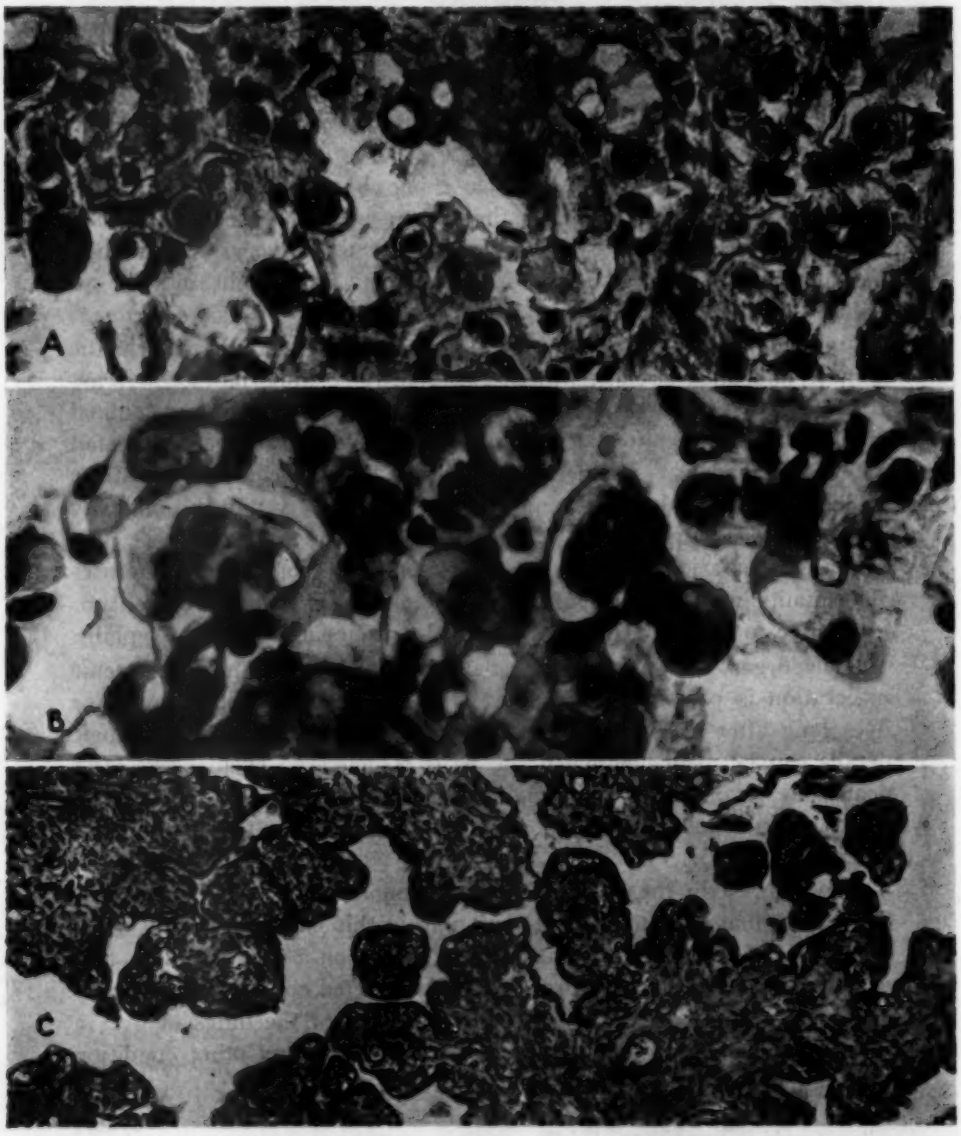

Fig. 2.—*A*, macerated lung with erythroblasts in pulmonary capillaries. *B*, nonmacerated lung with erythroblasts in pulmonary capillaries. *C*, placenta showing typical shape of villi in erythroblastosis fetalis.

variously called basophilic erythroblasts, megaloblasts and hemocytoblasts by different investigators (fig. 2 *B*). They are large in relation to the normal caliber of the pulmonary capillaries, and the appearance suggests that the cells are strained out of the general circulation and lodged in these vessels. It seems conceivable that these cells might interfere sufficiently with pulmonary circulation to be a factor in the death of some infants with this disease. An abnormal number of immature red blood cells in all stages of development are also found in the clots in the larger blood vessels, and although the cells often cannot be specifically identified, the fact that a disproportionately large number of nuclei are present is easily recognizable.

The erythroblasts within the pulmonary capillaries are early cells with large nuclei and little cytoplasm. They can ordinarily be easily distinguished from septal and connective tissue cells of the alveolar walls by their greater nuclear size and superior ability to retain dyes. These cells are characteristically found in this location only in the fetus and the newborn infant with erythroblastosis. Consequently the lung of the macerated fetus is ordinarily the one organ which will give histologic evidence of the disease. If only one tissue were available in the case of a macerated or nonmacerated fetus or liveborn infant, I believe a correct diagnosis could be made from the lung in a higher percentage of cases than from any other organ.

If the placenta is available, it is of great aid in establishing a diagnosis. When an infant is born alive with erythroblastosis, the placenta may show no gross or histologic deviation from normal, but if the disease is sufficiently severe to cause intrauterine death, the placenta is almost always abnormal. The total size and the weight are increased, and the cotyledons are large, thick and unusually well demarcated. The placenta undergoes degenerative changes much more slowly than the fetus, and frequently the villi are well preserved and can be subjected to histologic study long after this becomes impossible in most fetal organs. The villi are frequently enlarged (fig. 2 *C*). The stroma is edematous, and after fixation the loss of fluid from the interior may cause a loosening of the outer covering. Langhans' cells are often more numerous than they normally are and at times form an almost continuous layer of large hydropic cells beneath the syncytial covering. The cellularity of the stroma is often increased. The blood vessels are usually found near the peripheral margins of the villi, and although they may contain few blood cells, some immature red cells are almost always present. The vessels in the major villi frequently contain clots showing large numbers of nucleated cells.

SUMMARY

It is often difficult to arrive at a definite conclusion concerning the cause of death in a fetus that has died before the onset of labor. Careful gross examination combined with histologic study of the lungs will usually make it possible to diagnose erythroblastosis if it is present. The occurrence of erythroblasts in the pulmonary capillaries is the most important single diagnostic sign to be found in the macerated fetus. The placenta adds valuable corroboratory information and, if available, should always be examined.

The failure to demonstrate Rh in the erythrocytes of the mother is by itself insufficient evidence on which to base a diagnosis of erythroblastosis. Even in the presence of maceration a definite diagnosis can usually be made, but if any doubt exists, a positive diagnosis should be withheld. Unless there is conclusive evidence of erythroblastosis, the mother should not be advised against future child bearing.

HYPERTENSION AND NECROTIZING ARTERITIS IN THE RAT FOLLOWING RENAL INFARCTION

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AN EARLIER paper[1] presented a description of the circulating blood returning to infarcted renal tissue through reestablished vascular structures in the rat, and in conclusion it was mentioned that studies were in progress concerning the morphologic and functional alterations which result when the blood flows through such injured and dead tissue. These studies are described in the present report. Since they were undertaken to investigate the correspondence, if any, of functional or structural abnormalities occurring in the body of the rat with changes taking place in the renal infarct, the findings of that earlier work are briefly summarized here.

It was shown that soon after ligation and severance of a large branch of the renal artery it is possible for blood to enter the most distal glomeruli and arterioles of the severed artery from the neighboring tissue with an uninterrupted blood supply by way of the communicating intertubular capillary network of the two areas. After three days the main arterial stems of the infarcted area, as well as many of its glomeruli and intertubular capillaries, are open to the general circulation. At one week many more capillaries are patent, while at two weeks an extension of blood flow is observed in the previously only partly patent interlobular arteries, which in the interval have united to some extent with the intertubular network. At one month blood can flow throughout the entire necrotic mass in a continuously united sparse network of small vessels which join the main arteries and veins. Gradual absorption and shrinkage of the necrotic tissue occur. The shrinkage affects the vessels as well as the interstitial tissue, so that at the end of a year the area of infarction is a thin scar containing some fibrous tissue but consisting mainly of a vascular tissue which is recognizable as an evolution of the original vascular structures. The vessels joining the vascular system of the scar with that of the neighboring tissue are enlargements

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1. Loomis, D., and Jett-Jackson, C.: Arch. Path. **33**:735, 1942.

of the intertubular network which connects the glomeruli and arterioles of the two areas.

Since there are these communications, however small at the beginning, between the vessels of the neighboring uninvolved tissue and those of the infarct, it is possible for blood to flow into the affected area and degeneration products to drain from it into the venous system from the earliest moment of damage. Contact between the necrotic tissue and the circulating blood extends at an accelerating rate as blood flows through the increasing number of newly established or cleared pathways. This contact reaches a maximum and then diminishes with the shrinking of the necrotic mass by absorption. Throughout these continuously changing phases there must be quantitative and qualitative variations in the physical and the chemical structure of the dead tissue. Indeed, two such changes can be observed histologically, i. e., the precipitation of calcium, especially in the uppermost portions of the cortex, and the appearance of fat, particularly in the necrotic material of the glomeruli and proximal convoluted tubules.

On the basis of these facts the questions which I wish to explore in this study are:

1. Does renal infarction have effects on the circulatory system of the animal as evidenced by a functional disturbance, such as hypertension, or by structural changes, such as arterial lesions?

2. If so, can it be assumed that these effects are due to an agent absorbed from the infarcted area? What is the relation between the rate of development of the circulatory contact with the necrotic mass and the absorption of this and the rate of appearance and the degree and the duration of functional and structural changes?

3. Since infarction of necessity reduces the amount of renal tissue, does the reduction of this tissue account for some of the effects noted?

4. If so, what is the relative importance of the two factors, absorption of necrotic tissue and reduction of renal parenchyma?

EXPERIMENTAL MATERIAL

The rats used in the experiments weighed from 150 to 225 Gm. They were fed exclusively on Purina dog chow and given tap water to drink ad libitum. They fall into the following categories according to the experimental procedure:

Series 1 (rats with 100 per cent renal substance).—These were normal controls, with no operation; i. e., their kidneys were intact and free of infarction and are represented in charts and tables by two blank circles.

Series 2 (rats with 75 per cent renal substance).—These animals had undergone operative infarction of one half of one kidney, indicated in charts and tables by blackening of half of one of the circles.

Series 3 (rats with 50 per cent renal substance).—The animals were grouped according to the operations which they had undergone: (*a*) unilateral nephrectomy,

indicated by a single blank circle; (*b*) total infarction of one kidney, indicated by blackening of one of the circles; (*c*) infarction of one half of each kidney, indicated by blackening of half of each circle.

Series 4 (rats with 25 per cent renal substance).—These rats also were grouped according to the operations which had been performed on them: (*a*) subtotal nephrectomy-extirpation of one kidney and of half of the other, indicated in charts and tables by one-half blank circle; (*b*) subtotal nephrectomy and infarction. The operation included extirpation of one kidney and infarction of one half of the other, indicated by one circle, half blackened; (*c*) infarction of 75 per cent of renal tissue, infarction of one kidney and of one half of the other, indicated in charts and tables by one blackened circle and one half-blackened circle.

The circles mentioned as used in charts and tables represent kidneys; the blackened portion shows the amount of infarction.

OPERATIVE PROCEDURE

The technic used was the same as that described in a previous publication.[1] In every case of infarction the renal artery or one of its main branches was isolated, ligated in two places and cut between the ligatures. In group 4 *a* (subtotal nephrectomy leaving one-half kidney) the blood flow was arrested temporarily by placing a bulldog clamp on artery and vein while the poles were excised; the blood flow was restored immediately afterward by removing the clamp. The cut surface of the kidney was not cauterized.

MEASUREMENTS OF BLOOD PRESSURE

The blood pressure was measured in all animals by the indirect method of Byrom and Wilson[2] with some slight modifications. Glass was used instead of cellophane for the pressure chamber and Penrose tubing for the cuff. Also the procedure of measuring the blood pressure was varied somewhat. The rat's approximate blood pressure was roughly established and then carefully measured by raising the mercury level only 10 to 20 mm. above the expected point and letting it fall slowly until the sharp rise occurred in the plethysmograph. This was done to prevent collapsing the vessels by excessive pressure for periods long enough to cause retardation of the returning blood in the capillary bed.[3] Ether anesthesia was used.

It was discovered in trial tests that since the blood pressure falls during anesthesia and rises as the rat emerges, the point which most truly represents the the animal's blood pressure is uncertain. One reading is inadmissible, and an average of varying readings has no particular validity either, so that in the end the standard procedure described in the following paragraph was adopted. This procedure, though arbitrary, nevertheless permitted repetition and control and could be applied to every animal.

The animal was anesthetized sufficiently so that it could be adjusted to the apparatus and was laid on a cork platform kept warm by an electric lamp set at a standard distance above the animal. After the plethysmograph was adjusted, repeated measurements were taken until the rat's movements as it came out of anesthesia made it impossible to take more. The animal was then anesthetized again for sixty seconds, and readings were repeated until it began to move.

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2. Byrom, F. B., and Wilson, C. J.: J. Physiol. **93**:301, 1938.

3. Griffith, J. Q., and Farris, E. J.: The Rat, Philadelphia, J. B. Lippincott Company, 1942.

It was anesthetized a third time for sixty seconds, and measurements were repeated as before. An average of the five highest readings made while the animal was quiet in the three periods of anesthesia was the final figure taken for the blood pressure. Usually these five readings were within 1 to 6 mm. of each other, and in general the readings in each period repeated closely those of the other two. The readings within any one period, however, might vary from 10 to 20 mm. Kempf and Page [4] stated that with their method, a modification of that of Williams, Harrison and Grollman,[5] departures as great as 100 mm. from the average were noted. I found no such extreme variation, though sick animals may show a wider range than normal animals, the blood pressure either continuously dropping on successive anesthetizations or continuously rising.

Blood pressure measurements were made on all rats on at least one but usually on two occasions before operation, twenty-four hours later, and at weekly intervals thereafter. The blood pressure of a few animals was also measured at six, twelve and eighteen hours after operation and then daily during the first week.

DURATION OF EXPERIMENT

Animals were kept until they died, or if they lived for a year after operation, they were killed.

POSTMORTEM EXAMINATION

An autopsy was made on every rat, and sections of heart, lungs liver, spleen kidneys, intestines, pancreas and mesentery were fixed in both Zenker's fluid and a 10 per cent solution of formaldehyde. Hematoxylin and eosin and in some cases Masson and Weigert stains were made on the sections for microscopic study.

GENERAL OBSERVATIONS

Differences were observed in the several groups as regards blood pressure, pathologic changes and length of life.

Blood Pressure.—In normal rats the blood pressure when measured by these methods was found to vary from 74 to 156 mm. of mercury, with a mean of 110. Byrom and Wilson [2] estimated the normal pressure at 78 to 132 mm. of mercury, with a mean of 106. Figure 1 shows the findings of Williams, Wegria and Harrison [6] in regard to 1,207 normal rats when using an indirect method with unanesthetized animals, compared with all the preoperative readings of the experimental rats used in this study combined with all the weekly readings of the 11 controls, most of which lived a year or nearly a year after the experiments were started.

It was hoped by using ether anesthesia to eliminate the variability in blood pressure due to animal excitement. Day to day measurements showed only slight variation in normal animals; in weekly measurements the swings were more marked but had a tendency to follow a curve of

4. Kempf, G. F., and Page, I. H.: J. Lab. & Clin. Med. **27**:1192, 1942.

5. Williams, J. R.; Harrison, T. R., and Grollman, A.: J. Clin. Investigation **18**:373, 1939.

6. Williams, J. R.; Wegria, R., and Harrison, T. R.: Arch. Int. Med. **62**: 805, 1938.

gradual rather than precipitous increase and decrease. The blood pressure in some of the controls remained at a remarkably constant level for many weeks. Indeed, that of 1 animal varied less than 10 mm. in twenty weeks and not more than 5 mm. in eight weeks. No normal control animal showed throughout the entire year an elevation of more than 25 mm. above the initial blood pressure measurement, and the highest measurement of blood pressure obtained from controls was 158 mm., and this occurred only once. Therefore any rat with an elevation of blood pressure above 160 mm. of mercury or which showed an increase of more than 25 mm. above the preoperative level is considered hypertensive in these experiments.

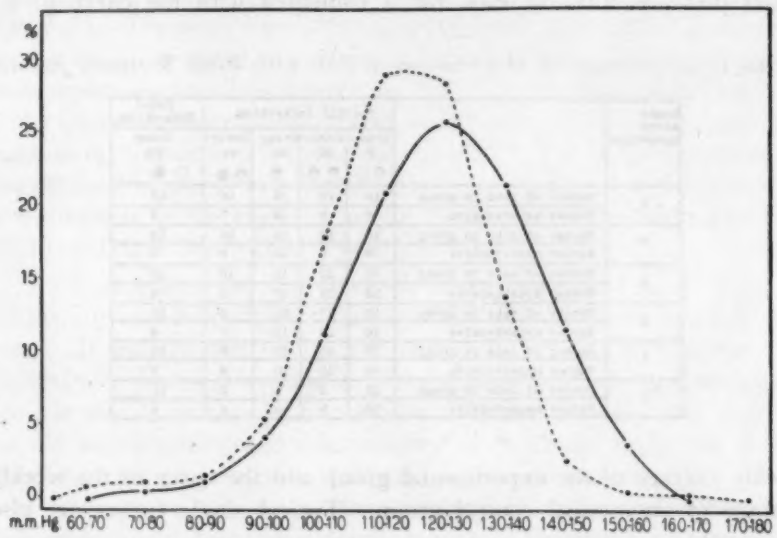

Fig. 1.—Curves showing the range of blood pressure in normal rats as determined by Williams, Wegria and Harrison [6] from the measurements of 1,207 animals (- - - - -) and as determined in the present study from 647 measurements of 100 animals (————)

Hypertension developed in a high percentage of the rats with renal substance reduced, whether by infarction or by extirpation (fig. 14). Only a general statement of certain characteristics of the hypertension needs to be made at this time, for the details of the effect of each of the various operations on blood pressure will be analyzed later. Hypertension did not develop in most animals until after some weeks (see table 1); therefore no animals that died in less than three weeks are included in the consideration of hypertension. The highest blood pressure measured was 262 mm. of mercury, and pressures above 220 mm. were not uncommon. The hypertension which persisted longest was observed to the end of the experiment at one year. In some hypertensive rats

the pressure declined to lower levels or became normal before the end of the experiment. Sharp drops and elevations occurred fairly frequently, and often a precipitous fall to a very low level immediately preceded death. Differences were also observed in the rate of development of hypertension and in the general form of the blood pressure curves with the duration of the experiment, and these differences appear to have significance.

It is evident that critical evaluation of such varying data is possible only when the evidence is available in its entirety. For this reason all the characteristics of the blood pressure readings may be seen in the complete data presented in figures 8 to 15, inclusive. Here the individual blood pressure curve of each rat is compared with the curve of the

TABLE 1.—*Development of Hypertension in Rats with Renal Substance Reduced*

Weeks after Operation		Partial Infarction				Total Infarction
		Group 2 ◓ ○	Group 3c ◓ ◓	Group 4b ◓	Group 4c ◓ ●	Group 5b ○ ●
1	Number of rats in group	10	10	11	10	12
	Number hypertensive	6	9	10	7	2
2	Number of rats in group	10	10	11	10	12
	Number hypertensive	6	9	10	9	2
3	Number of rats in group	10	10	11	10	12
	Number hypertensive	10	10	10	9	2
4	Number of rats in group	10	10	11	8	11
	Number hypertensive	10	10	10	7	4
5	Number of rats in group	10	10	10	8	11
	Number hypertensive	10	10	10	6	5
6	Number of rats in group	10	9	8	5	11
	Number hypertensive	10	9	8	5	6

weekly average of the experimental group and the curve of the weekly average of the normal control group. Typical single curves are also presented.

Vascular Lesions.—Vascular lesions similar to those observed in rats by Wilson and Byrom [7] after compressing a renal artery, by Friedman, Jarmon and Klemperer [8] after applying cellophane to one kidney and by others [9] after performing similar procedures on rats or other animals occurred frequently in several groups.

7. Wilson, C. J., and Byrom, F. B.: Quart. J. Med. **10**:65, 1941.

8. Friedman, B.; Jarmon, J., and Klemperer, P.: Am. J. M. Sc. **202**: 20, 1941.

9. (*a*) Cromartie, W. J.: Am. J. M. Sc. **206**:66, 1943. (*b*) Child, C. G.: J. Exper. Med. **67**:521, 1938. (*c*) Goldblatt, H., and Kahn, J. R., in Publication 13, American Association for the Advancement of Science, 1940, p. 266. (*d*) Wilson, C., and Pickering, G. W.: Clin. Sc. **3**:343, 1938. (*e*) Smith, C. C.; Zeek, P. M., and McGuire, J.: Am. J. Path. **20**:721, 1944. (*f*) Schroeder, H. H., and Neuman, C.: J. Exper. Med. **75**:527. 1942.

The lesions were most frequent and most extreme in degree in the mesenteric vessels but occurred also, in severely affected animals, in all of the other abdominal and pelvic arteries except the aorta. The smaller arteries and arterioles of the heart and the kidney were next most frequently affected, while those of the liver, the spleen and the lungs were involved only rarely.

The skeletal muscles and the central nervous system were not examined, so that the incidence of the vascular lesions in those areas is not known. Cyanosis of the foreleg developed in 1 animal, and dissection on its death revealed that the brachial artery was extensively involved.

In extreme examples the affected arteries were strikingly altered (fig. 2 *A*). The walls were irregularly thickened and nodular in appearance, with aneurysmal dilatations and tortuosities. On section they were sometimes found to contain thrombi. In animals which died late in the course of the experiments or which were killed at one year the walls were fibrous and occasionally calcified. The process sometimes was confined to one or two fibrous or calcified nodules found exclusively in the vessels of the tissue attaching the pancreas and the duodenum (and could have been easily missed unless searched for).

Microscopically, the lesion in its acute stage was seen to be a necrotizing and inflammatory process involving all three coats of the vessel. It was characterized by necrosis of the intima (fig. 2 *B* and *C*), deposits of subintimal hyaline or fibrinoid masses which often extended into the media, necrosis of the muscle cells of the media (fig. 2 *B, C* and *D*) and shredding and disappearance of the elastic tissue (fig. 3 *B*). All coats were progressively infiltrated with quantities of cells. These were neutrophilic leukocytes, many eosinophils, and mononuclear cells with ovoid nuclei containing deeply basophilic chromatin masses (figs. 2 *D* and 3 *A*). In acute lesions thrombi were often fused with the fibrinoid material of the intima. The lesion progressed to a granulomatous stage, fibroblasts and capillaries penetrating to the intima, sometimes in a radial arrangement, while in the outer portions the young connective tissue and capillaries were more or less concentrically arranged (fig. 3 *A*). In the granulation tissue there were lymphocytes and plasma cells. Hemorrhages were present in the involved arterial wall, and deposits of hemosiderin were common.

In some arteries the inflammatory condition appeared to subside with little residue beyond fibrosis of the adventitia. In others, the muscle cells did not regenerate, and the walls were composed entirely of connective and elastic tissue. The elastic tissue either fragmented and disappeared (fig. 3 *B*) or was increased and dispersed throughout the whole wall as in figure 4 *A*. The necrotic areas in the media were

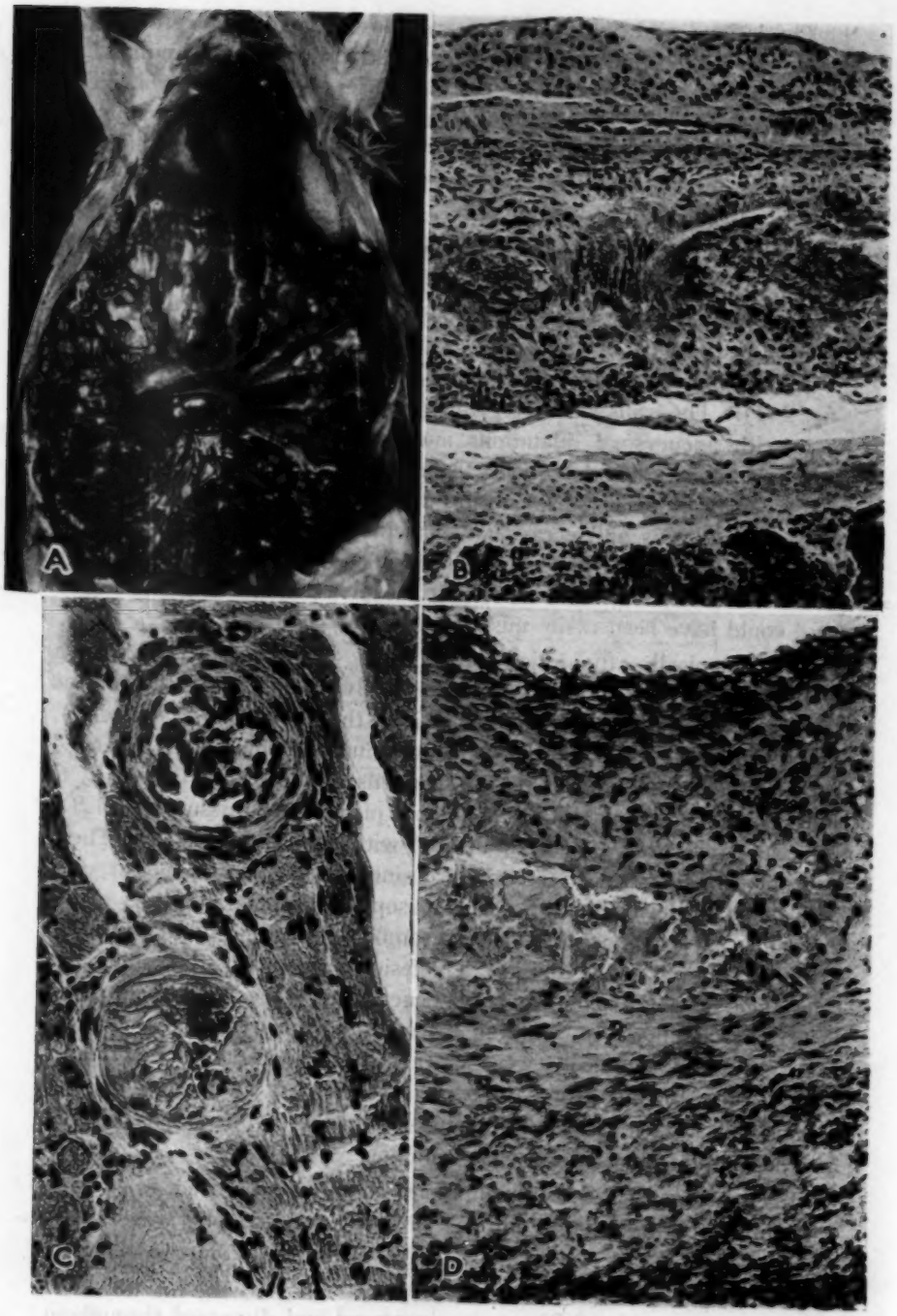

Figure 2

(See legend on opposite page)

not infrequently the seat of calcium deposits (fig. 4 *B*; compare with fig. 2 *D*). On healing, the granulation tissue in and around the adventitia became in the end dense collagenous tissue (fig. 4 *D*), the thrombi were organized and the lumens of the arteries were completely occluded.

Other modifications in the structure of the arteries and the arterioles took place, such as proliferation of the endothelium which almost filled the lumen (fig. 2 *C*), focal proliferation of subendothelial connective tissue with elastic tissue ramifying between the connective tissue cells (fig. 5 *A*) and hypertrophy of the media (fig. 5 *B*).

These changes in some cases appeared to be arrested and healed; in others healing and new lesions were encountered even as late as one year after the experimental infarction, the acute lesions being superimposed on an older process.

Parenchymal Lesions.—(*a*) Heart: In severe involvements the lesions of the cardiac muscle could be detected with the naked eye, appearing as white patches with linear streaks. The lesions were most commonly found in the right auricle but were also observed in the left ventricle and frequently at or near the apex.

Microscopically, these streaks were seen to be areas of necrosis of muscle fibers, in which there was sometimes hemorrhage and into which many cells of mononuclear type had infiltrated (fig. 5 *C*). Plasma cells and lymphocytes were present, but the chief cell was one with a large round or ovoid nucleus and little cytoplasm. Polymorphonuclear cells were usually absent or, if present, were few. Necrotizing arteritis and arteriolitis were observed in the coronary vessels, and these vascular lesions were often, but not always, seen in close relation to the lesion of the muscle.

Sometimes infiltration with mononuclear cells was observed in the absence of necrosis of the cardiac muscle cells, and among the infiltrating cells were some of the type known as Anitschkow myocytes. The latter

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EXPLANATION OF FIGURE 2

A, gross aspect of the lesions of the mesenteric arteries, showing the nodular thickening, tortuosity and dilatation. Rat P-15 of group 4 *c* (one kidney and half of the other showing complete infarction) at seventeen weeks.

B, mesenteric artery showing necrosis of media and intima. The subintimal fibrinoid mass is fused with that in the lumen. There is a periarterial infiltration of inflammatory cells. Rat P-59 of group 3 *c* (one half of each kidney showing complete infarction) at one week. × 150.

C, necrosis of arterioles in the heart muscle. The fibrinoid mass completely fills the lumen of each of the lower vessels. The vessel at the top shows proliferation of the endothelium. Rat P-49 of group 4 *c* (one kidney and half of the other showing complete infarction) at four weeks. × 300.

D, mesenteric artery showing necrosis of media, proliferation of endothelium and infiltration of all coats with inflammatory cells. Rat P-88 of group 4 *c* (one kidney and half of the other showing complete infarction) at three weeks. × 150.

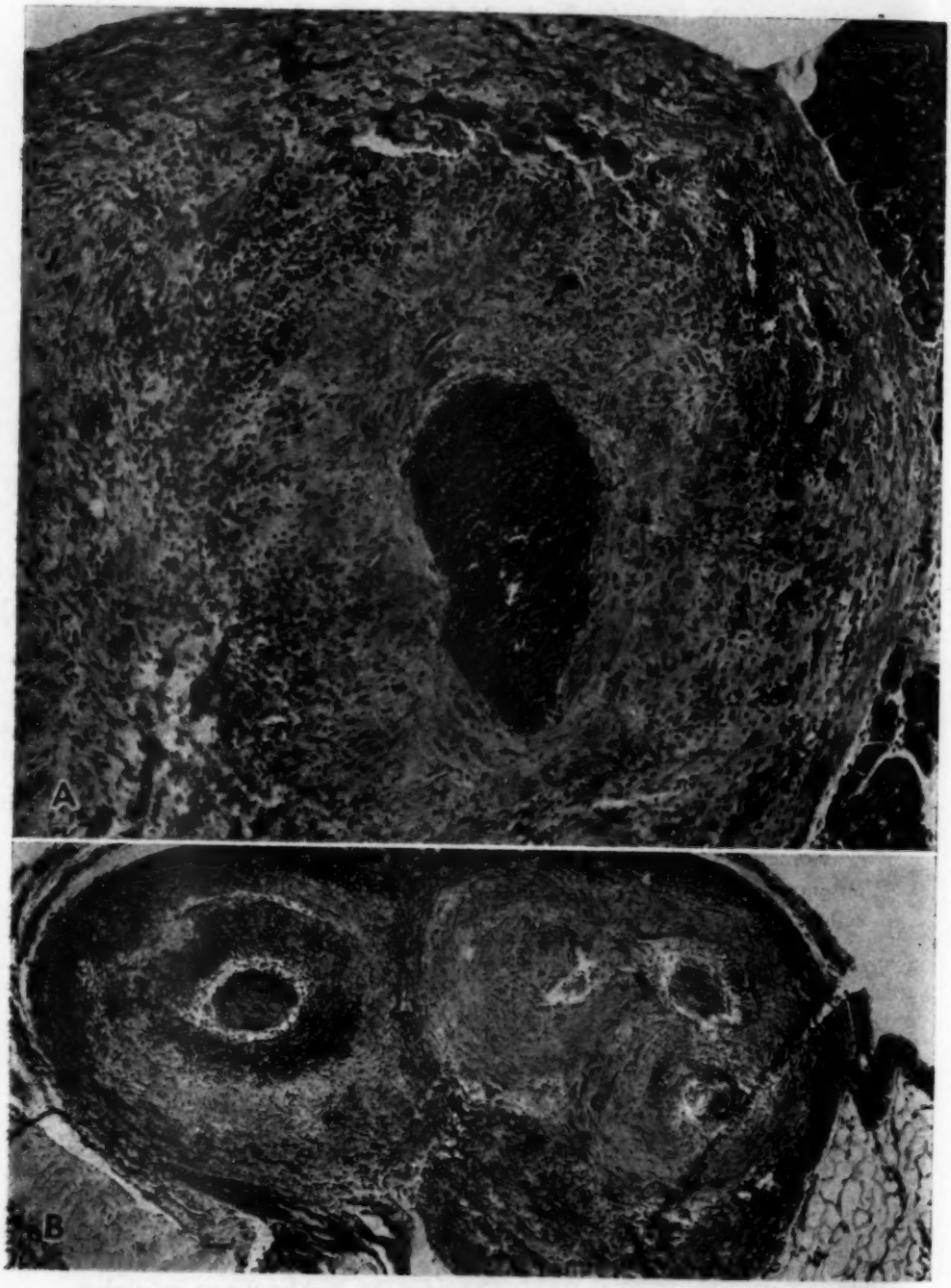

Figure 3

(See legend on opposite page)

were also seen in small collections in the endocardium and in the adventitia of the coronary vessels in arrangements resembling Aschoff bodies (fig. 5 *D*). Fibrous tissue proliferation ramified through the involved areas, and in later periods fibrous scars of varying sizes were observed in the myocardium.

(*b*) Kidney: The changes in the uninfarcted portion of the renal tissue aside from hypertrophy varied from an occasional scar and a few dilated tubules to extreme damage, as seen in figures 6 *B* and *C*. Such extreme changes were observed only in those three groups which had had the renal substance reduced to 25 per cent of the original total by infarction or excision or both, and in only a portion of the animals in these groups. Rats of these groups dying early showed beginning dilatation of tubules and cast formation as early as five weeks after operation (fig. 6 *A*), and these changes became progressively more marked in rats dying later. The extreme distention of the tubules with masses of hyaline material such as is shown in figure 6 *B* and *C* was not observed until eighteen weeks or later. In a few animals of each of the three aforementioned groups the renal lesion did not develop, the remnant of kidney apparently compensating sufficiently to prevent it.

The characteristic changes in the tubules of the nephrons are therefore the so-called degenerative lesions, consisting of cystic dilatation of the tubules, distention by casts, parenchymatous and fatty degeneration, compression atrophy of the epithelium in the distended tubules and desquamation of epithelial cells.

The altered glomeruli in the involved regions were large, pale staining and anemic and often completely filled Bowman's capsule. The capsular space, if not obliterated, was dilated and filled with coagulated material, and the capsular membrane was swollen and thickened. There was little or no blood in the capillaries of the tuft, and its tissues showed fewer nuclei than usual, while the epithelial cells of its membrane were large and swollen and contained foamy cytoplasm (fig. 6 *D* and *E*). Small aggregations of cells proliferating at one side of the capsule and somewhat resembling a glomerular crescent were observed in some cases.

EXPLANATION OF FIGURE 3

A, massive increase in the thickness of the wall of a mesenteric artery. Little of the original structure is left. Note that periarterial fibrosis, infiltration of granulation tissue with inflammatory cells and fibrinoid necrosis can all be found in this section. Rat P-10 of group 4 *c* (one kidney and half of the other showing complete infarction) at thirteen weeks. × 133.

B, section of three branches of a mesenteric artery. The vessels at the right show almost complete disappearance of elastic tissue; the one at the left shows this tissue in fragmented and widely scattered strands. Rat P-32 of group 2 (one half of one kidney showing complete infarction) at fifty-two weeks. × 53.

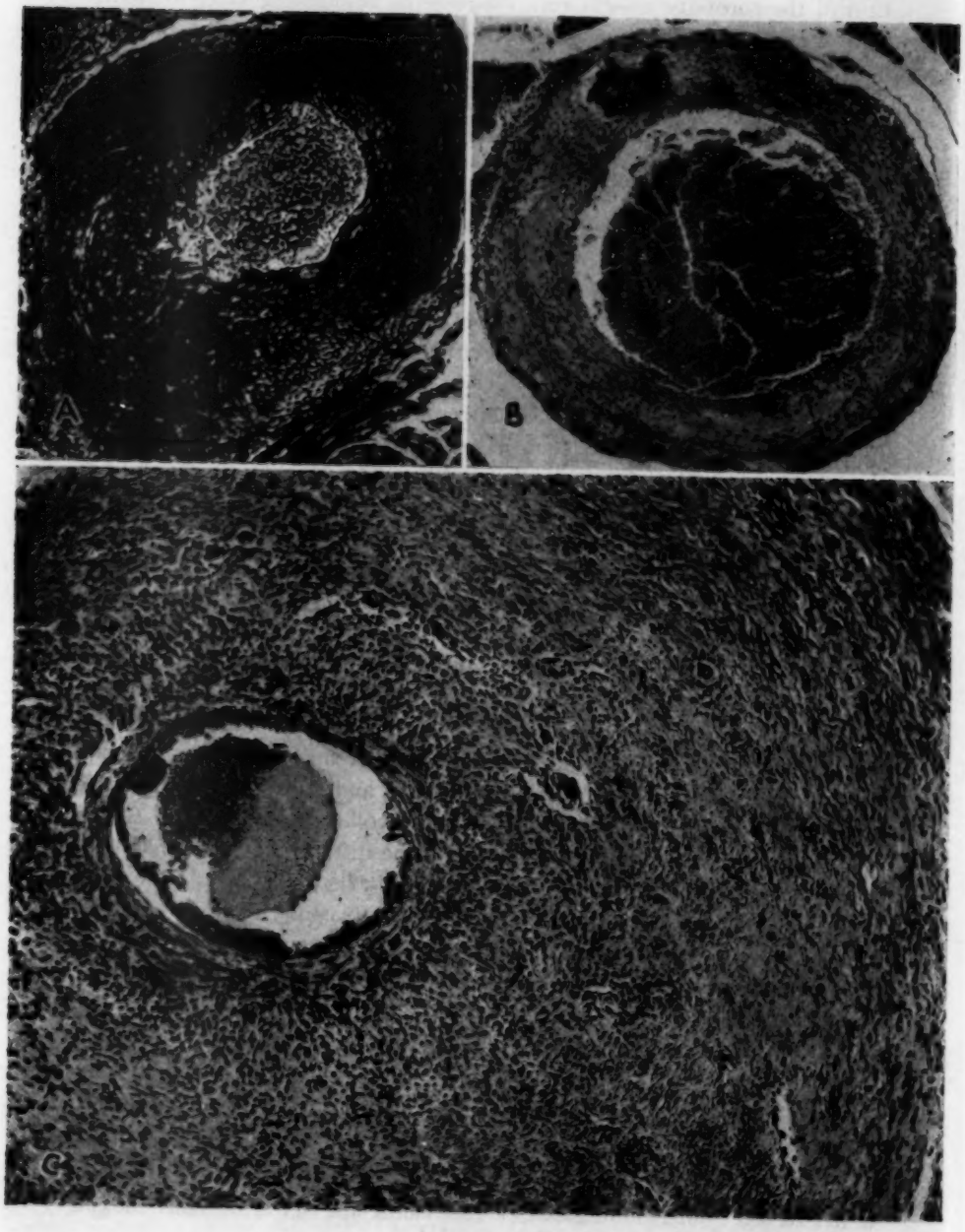

Figure 4

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Necrotizing arteritis and arteriolitis also occurred in the kidney (fig. 6*F*). They were noted almost entirely in the groups of animals with infarcted kidneys and were not seen in the group with unilateral nephrectomy, nor in the controls. They were seen as early as one week and as late as one year and in kidneys with and without the parenchymal changes described in foregoing paragraphs. Infiltration of the arterial coats with inflammatory cells was not present in the intrarenal arteries, and no fresh infarcts or wedge-shaped scars of infarcts that could have been the result of these vascular lesions were found.

Besides the acute necrotizing vascular lesion just described, marked hyaline thickening of the walls of the interlobular arteries and afferent arterioles occurred in some cases, the lumens of the vessels being almost obliterated. This was observed in the kidneys of those rats which had great reduction of renal substance, high blood pressure and marked parenchymatous changes in the renal remnant. Focal lymphocytic infiltrations and some increase in interstitial connective tissue occurred around the atrophic tubules and glomeruli in these kidneys.

The appearance of the infarcts that had been produced to initiate the experiment varied according to the time of death of the animal. Examination of kidneys of rats dying at fifteen and eighteen weeks showed that absorption of necrotic debris was not yet complete. By twenty-six weeks the tissue was about as condensed as at fifty-two weeks, with nothing remaining but calcium masses, a little connective tissue, blood vessels and a few remnants of collecting tubules. Atrophic but well preserved glomeruli persisted at the borders of the infarct.

Length of Life After Operation.—Death not infrequently occurred soon after operation in those groups which had undergone a double operation and which were deprived of most of their renal tissue. Of the total number of 100 rats operated on, 17 lived a week or less, and 5 lived between two and three weeks. These were not included in the consideration of length of life after operation, only such animals being

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EXPLANATION OF FIGURE 4

A, dense and irregular spread of elastic tissue throughout the wall of a mesenteric artery. Rat P-32 of group 2 (one half of one kidney showing complete infarction) at fifty-two weeks. × 53.

B, deposit of calcium in the media of a pancreatic artery. Compare the area of deposition with the area of necrosis shown in figure 2*D*. Rat P-62 of group 2 (one half of one kidney showing complete infarction) at fifty-two weeks. × 53.

C, mesenteric artery showing collagenization of periarterial tissue and the presence of many capillaries in the vessel wall The original vascular tissue has been completely replaced by connective tissue. Rat P-70 of group 4*b* (one kidney extirpated and half of the other showing complete infarction) at twenty-four weeks. × 133.

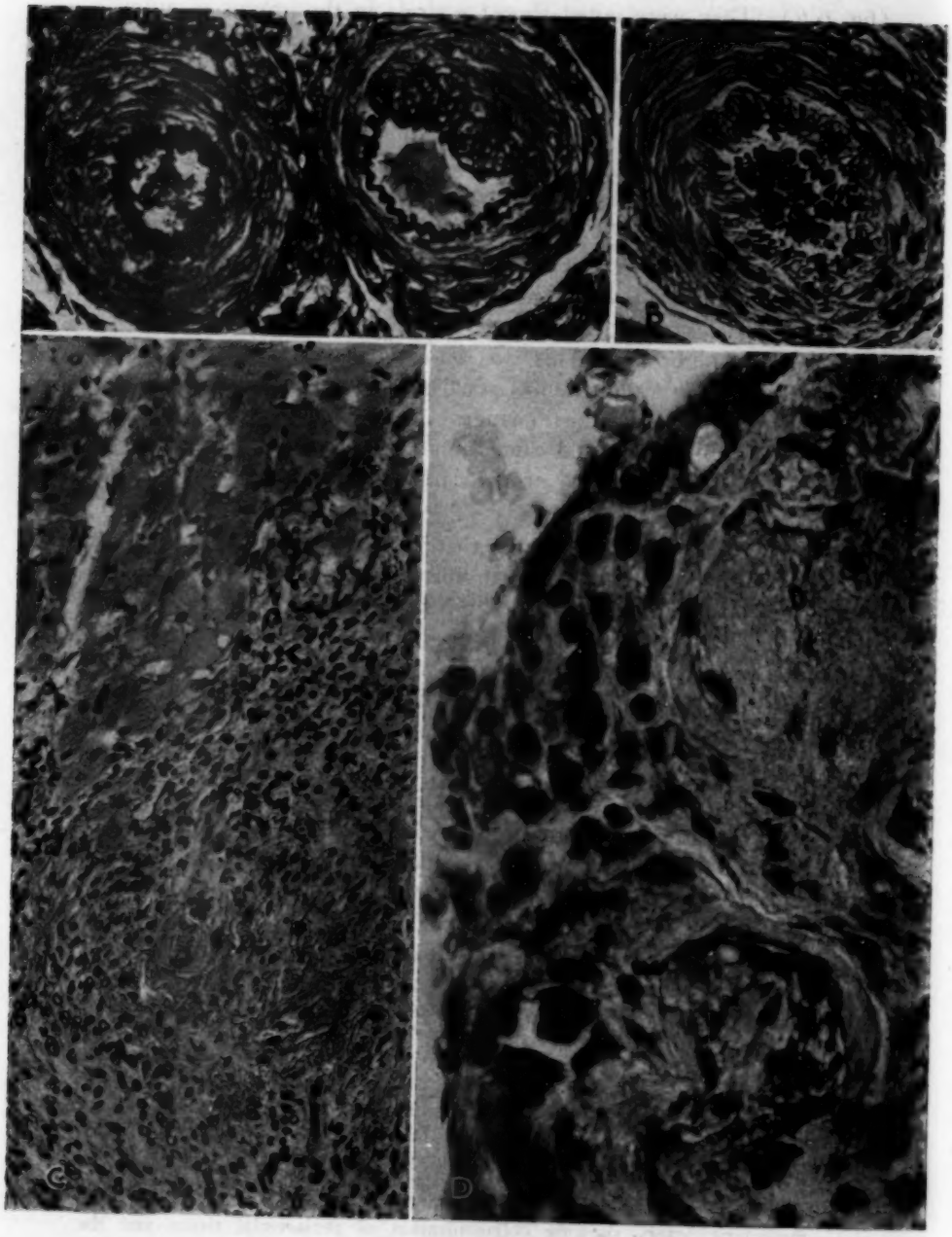

Figure 5

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used for this purpose as had lived three weeks or longer, a period corresponding to the limits set for the consideration of hypertension. It was felt that the effect of intercurrent disease on the length of life after operation as well as on blood pressure was too indefinite a quantity to assay, although it was quite obvious at autopsies that the deaths of some animals were due at least partly to such conditions as chronic pneumonia with bronchiectatic abscesses, acute pneumonia, cecitis and neoplasms. However, deaths which could be ascribed to those conditions occurred chiefly in the latter part of the experiments and do not have the significance of the earlier deaths. The controls, as well as the animals used in the experimental procedures, showed these diseases. None of the controls, however, exhibited the condition reported by Moore and Hitchcock [10] and called chronic nephrosis by Saxton and Kimball [11] or the vascular disease found in old animals by Wilens and Sproul.[12] The oldest animals were approximately 18 months old at the time the experiments were terminated.

The deaths at various intervals throughout the experimental period appeared roughly to group themselves into those occurring in an early and those in a late stage with six months, i. e., twenty-six weeks, as the dividing line. In the latter group are included the rats which survived to the end of the experimental period of one year and were then killed. The distribution of deaths is shown in figure 7.

There were seven accidental deaths due to overanesthetization. When it is considered that this small number occurred in more than 3,000 opportunities, the risk of the method does not seem great, and even these few deaths could have been avoided by closer attention. Since most

10. Moore, R. A., and Hitchcock, F. A.: Proc. Soc. Exper. Biol. & Med. **27**:206, 1930.

11. Saxton, J. A., and Kimball, G. C.: Arch. Path. **32**:951, 1930.

12. Wilens, S. L., and Sproul, E. E.: Am. J. Path. **14**:177 and 201, 1938.

EXPLANATION OF FIGURE 5

A, small vessels of the mesentery showing thickening of their walls. The one at the right show elastic tissue fibrils ramifying was in the focal proliferation of subendothelial tissue. Rat P-32 of group 2 (half of one kidney showing complete infarction) at fifty-two weeks. × 250.

B, hyperplasia of muscle cells in the media of a mesenteric arteriole. Rat P-32 of group 2 (half of one kidney showing complete infarction) at fifty-two weeks. × 375.

C, microscopic view of a lesion in the myocardium. Note an area of necrosis of muscle cells with infiltration of inflammatory cells. Rat P-59 of group 3 *c* (half of each kidney showing complete infarction) at one week. × 250.

D, cellular aggregation in endocardium resembling an Aschoff body. Rat P-49 of group 4 *c* (one kidney and half of the other showing complete infarction) at four weeks. × 666.5.

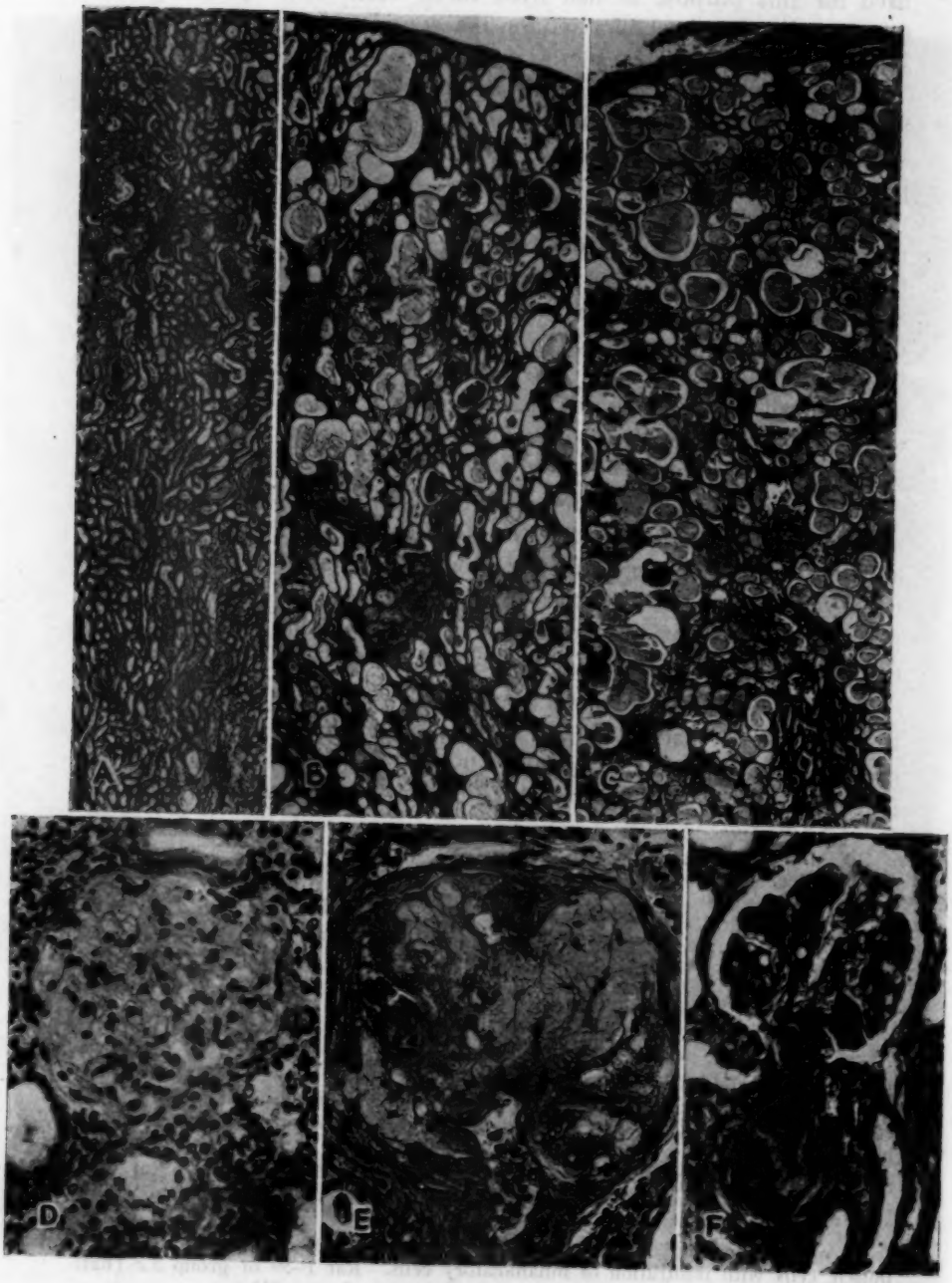

Figure 6

(See legend on opposite page)

of them occurred late in the experimental period, the deaths have no great weight in the percentages presented in figure 14.

RESULTS IN EACH EXPERIMENTAL GROUP

Series 1 (controls: animals with 100 per cent of their renal substance).—In the controls, with no operation, the blood pressure was never elevated above 160 mm. of mercury, though in later months there was a tendency in some for it to be slightly elevated above the original level. A curve which is typical of this group is shown in figure 8 *A*; all the individual and the mean curves for the group are shown in figure 9 *A*. There were no arterial lesions. One animal, or 9 per cent of these rats, died before six months; 54 per cent lived one year.

Series 2 (animals with 75 per cent of their renal substance, one kidney being one-half infarcted).—In 100 per cent of the animals the blood pressure was elevated above 160 mm. of mercury, and 30 per cent showed blood pressures above 200. After a sustained elevation of several months, although there was some variability in the curves, there was a general tendency toward a drop in blood pressure. This is shown in a typical animal in figure 8 *B*. All the individual and the mean curves for the group are shown in figure 9 *B*. Fifty per cent

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EXPLANATION OF FIGURE 6

A, section of kidney of a rat deprived of 75 per cent of its renal tissue by infarction. Note the beginning dilatation of tubules and the granular precipitate in their lumens. Rat P-16 of group 4 *c* (one kidney and half of the other showing complete infarction) at five weeks. × 26.

B, section of kidney of a rat deprived of 75 per cent of its renal tissue partly by infarction and partly by extirpation. The greatly dilated tubules have flattened epithelium and contain masses of hyaline material. In some areas, the tubules are atrophic, and there is an increase in connective tissue. Rat P-29 of group 4 *b* (one kidney extirpated and half of the other showing complete infarction) at eighteen weeks. × 26.

C, section of renal cortex from a rat deprived of 75 per cent of its renal tissue by extirpation. The same parenchymal changes are observed here as in *B*. Rat P-105 of group 4 *a* (one kidney and half of the other extirpated) at thirty-four weeks. × 26.

D, glomerulus from the same kidney as the section shown in *A*. The capillary loops are fused. The capsular space is obliterated, and there is thickening of the capillary and capsular membranes. Rat P-16 of group 4 *c* (one kidney and half of the other showing complete infarction) at five weeks. × 261.

E, glomerulus from the same kidney as the section shown in *B*. Note large foamy epithelial cells, fused capillary loops, thickening of Bowman's capsule and thickening of the wall of an afferent arteriole. Rat P-29 of group 4 *b* (one kidney extirpated and half of the other showing complete infarction) at eighteen weeks. × 261.

F, necrosis of the wall of an afferent arteriole with dilatation and thrombosis. Rat P-124 of group 4 *c* (one kidney and half of the other showing complete infarction) at two weeks. × 261.

of the rats had arterial lesions, 20 per cent showing alterations of a severe nature. The occurrence of vascular lesions did not correspond with the occurrence of high blood pressure. Since all but 1 of the animals survived for a year after operation, the vascular lesions found in this group were mostly healed or healing, although an occasional acute lesion was found as late as a year after infarction. There were

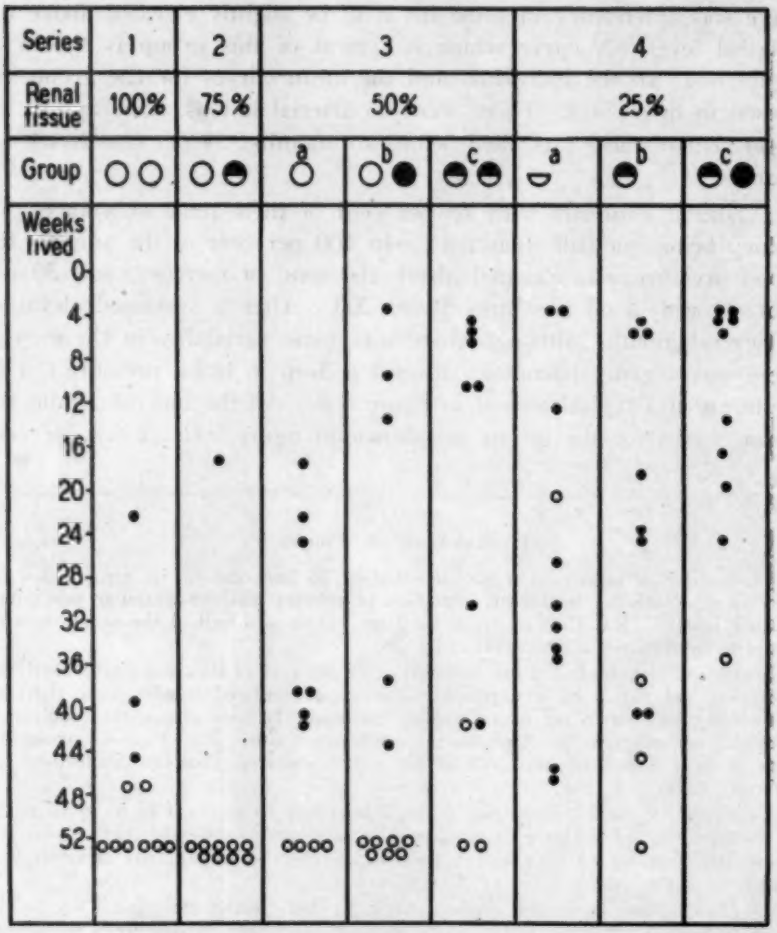

Fig. 7.—Chart showing time when death occurred in all rats living three weeks or longer after operation. Death by anesthesia ○; animal found dead ●.

no changes in the intact renal tissue beyond moderate hypertrophy. One animal of the group, or 10 per cent, died before six months. Ninety per cent lived one year.

Series 3 (animals with 50 per cent of their renal substance).—(*a*) One kidney extirpated: In 2 of the 11 animals in this group the

blood pressure showed sporadic elevations reaching between 170 and 180 mm. of mercury (fig. 10 *A*), while in 2 others the blood pressure reached 160 mm. only once. The pressure curves of the remainder resembled those of the controls. All the individual and the mean curves are shown in fig. 11 *A*. None of these rats had arterial lesions. There was no alteration except hypertrophy in the remaining kidney. Twenty-seven per cent of the rats died before six months; 37 per cent lived one year.

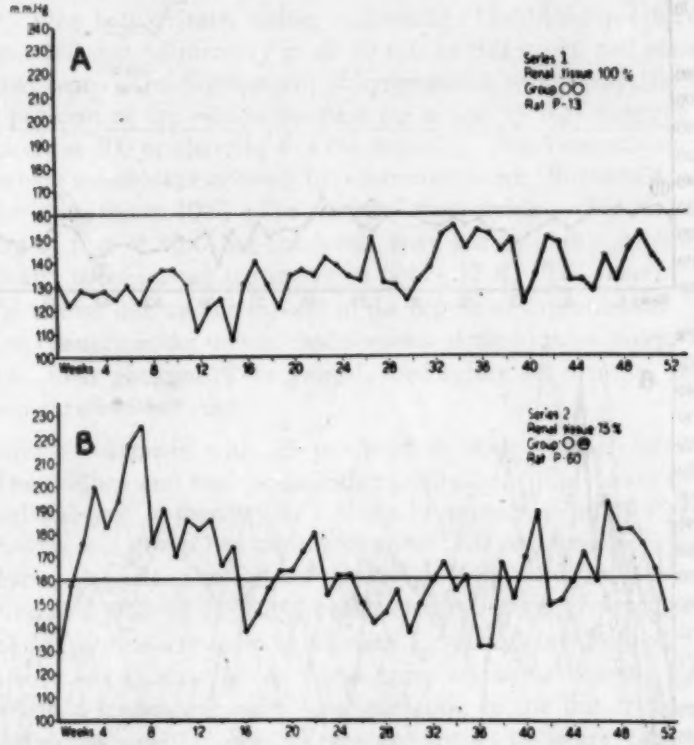

Fig. 8.—Blood pressure curves of individual rats in series 1 and 2. *A*, series 1 (control with both kidneys normal). *B*, series 2. Circles represent kidneys; black shading represents infarction.

(*b*) One entire kidney infarcted: The blood pressures in this group were variable. In 50 per cent of the animals the blood pressure was never above 160 mm. of mercury. Of the 6 animals which were hypertensive, 1 had a blood pressure of 160 mm. on one occasion, 1 died after hypertension of eleven weeks' duration, the pressure ranging around 170 mm. of mercury, and the blood pressure of the 4 remaining rats reached levels between 170 and 210 mm. and declined to a lower level during the latter part of the year (fig. 10 *B*). All the individual

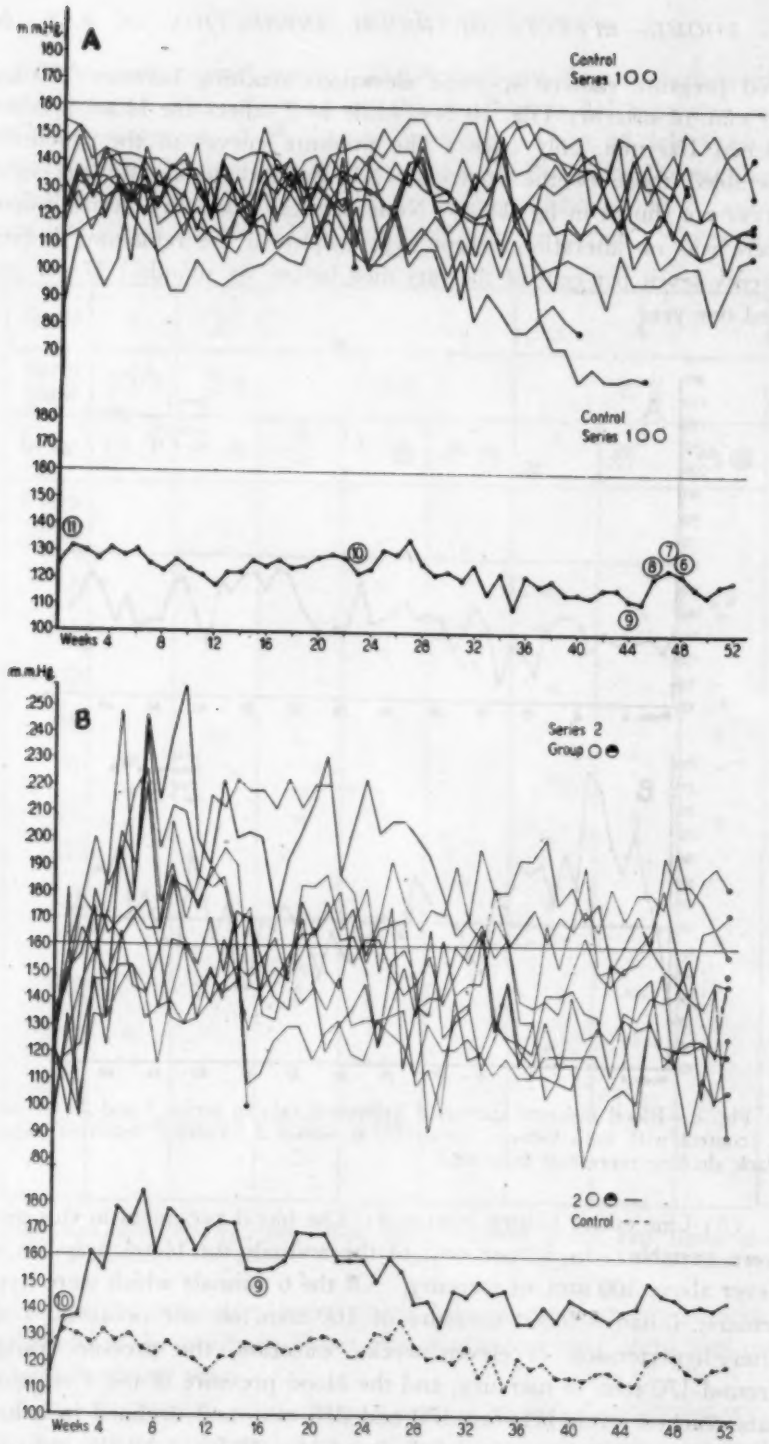

Figure 9

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and the mean curves are shown in figure 11 *B*. Arterial lesions occurred in 25 per cent and were moderately severe in only 1 animal. There was no correspondence between degree and duration of hypertension and occurrence of arterial lesions. The 1 animal in which moderately severe arterial lesions developed died at nine weeks without showing hypertension, while the 2 animals with hypertension above 200 did not show vascular lesions. There were no changes in the uninfarcted kidney except hypertrophy. Three, or 25 per cent, of the animals died before six months. Seven, or 68.3 per cent, lived one year.

(*c*) One half of each kidney infarcted: The blood pressure rose to about 160 mm. of mercury in all 10 rats in this group and above 200 in 40 per cent. The development of hypertension was prompt, occurring in 90 per cent of the rats in the first week, and by that time the blood pressure was 200 or above in 4 of the animals. The 5 animals surviving more than six months showed hypertension which diminished in later months. See figure 10 *C*. The curve of those dying earlier was similar in form to that of 13 *C* but the levels were not so high. All the individual and mean curves are shown in figure 12 *A*. The severity of the arterial lesions did not correspond to the degree of hypertension. There were no changes in the uninfarcted portions of the kidneys except hypertrophy. Fifty per cent of the animals died before six months. Twenty per cent survived one year.

Series 4 (animals with 25 per cent of their renal substance).—(*a*) One kidney and half of the other extirpated: The blood pressure reached 160 mm. of mercury in 5 of the 11 animals, or in 45.4 per cent. No rats in this group had pressures above 200 mm. and only 1 above 180 mm. Hypertension did not develop in the first weeks after operation, the first affected animal showing elevated blood pressure at seven weeks. A typical curve in this group is represented by figure 13 *A*. Even in those animals whose blood pressures never rose to 160 mm. there was a tendency toward some elevation in the last months. All the individual and the mean curves are shown in figure 13 *B*. Mild vascular lesions were found in 81 per cent of the animals. Sometimes these consisted of a single nodule.

Fig. 9.—Blood pressure curves of all rats in control series 1 and series 2.

In this figure and in figures 11, 12, 14 and 15, the upper part of each chart shows individual curves; the lower part, the curve for the average of blood pressures. The symbol • ending a curve means that the animal died. The symbol ○ ending a curve means that the animal was killed. The encircled figures in each chart that shows average curves represent the number of animals in the experiment as it progressed. The average of the controls is shown by a broken line in all except figure 11 *A*. Circles represent kidneys; black shading represents infarction.

Besides hypertrophy, there were marked changes in the kidney remnant in 7, or 63 per cent, of the animals, while slight changes were observed in 2 and none in 2 animals that died at three weeks. Five,

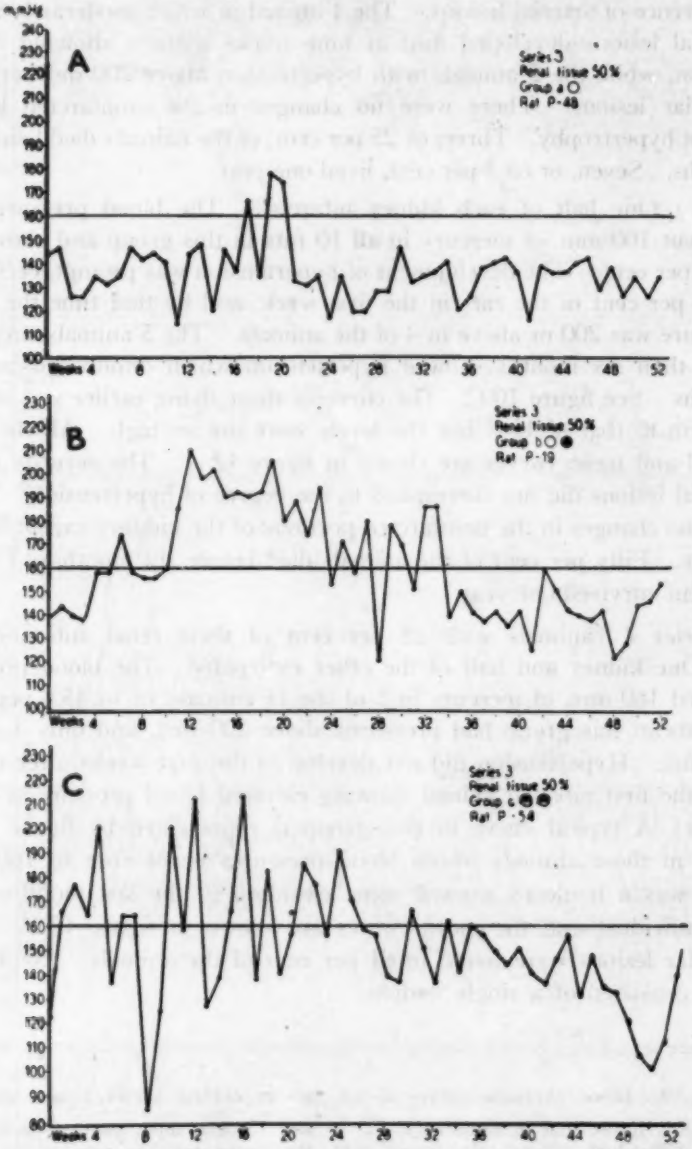

Fig. 10.—Blood pressure curves of individual rats in series 3. *A*, *B* and *C*, series 3, groups *a*, *b* and *c*, respectively.

or 45 per cent, died before six months. None survived for one year. The 2 rats living the longest died in the forty-sixth week.

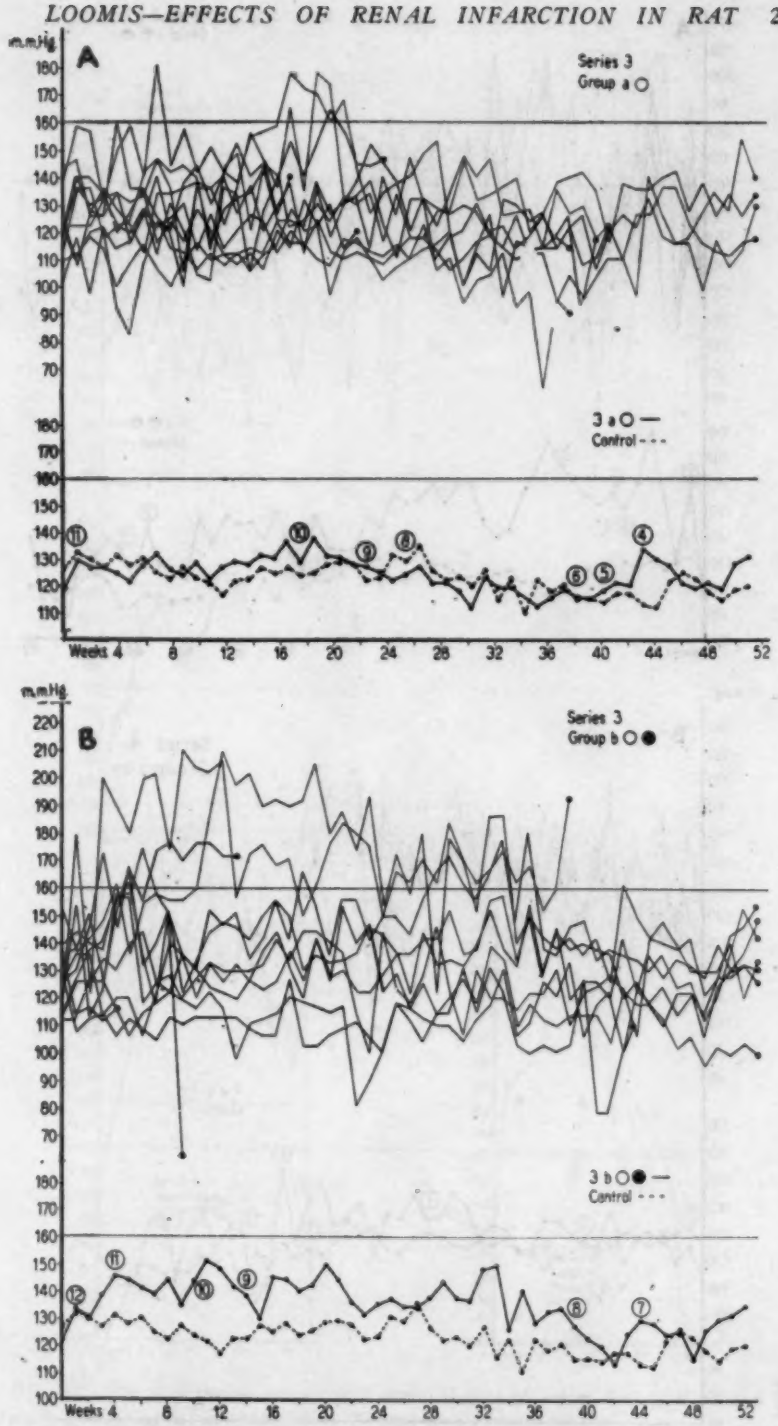
A
Series 3
Group a ○
3 a ○ —
Control - - -
m.m.Hg
Weeks 4 8 12 16 20 24 28 32 36 40 44 48 52
B
Series 3
Group b ○ ●
3 b ○ ● —
Control - - -
m.m.Hg
Weeks 4 8 12 16 20 24 28 32 36 40 44 48 52

Fig. 11.—Blood pressure curves of all rats in group *a* and group *b* of series 3. (See the legend of figure 9 for further explanation.)

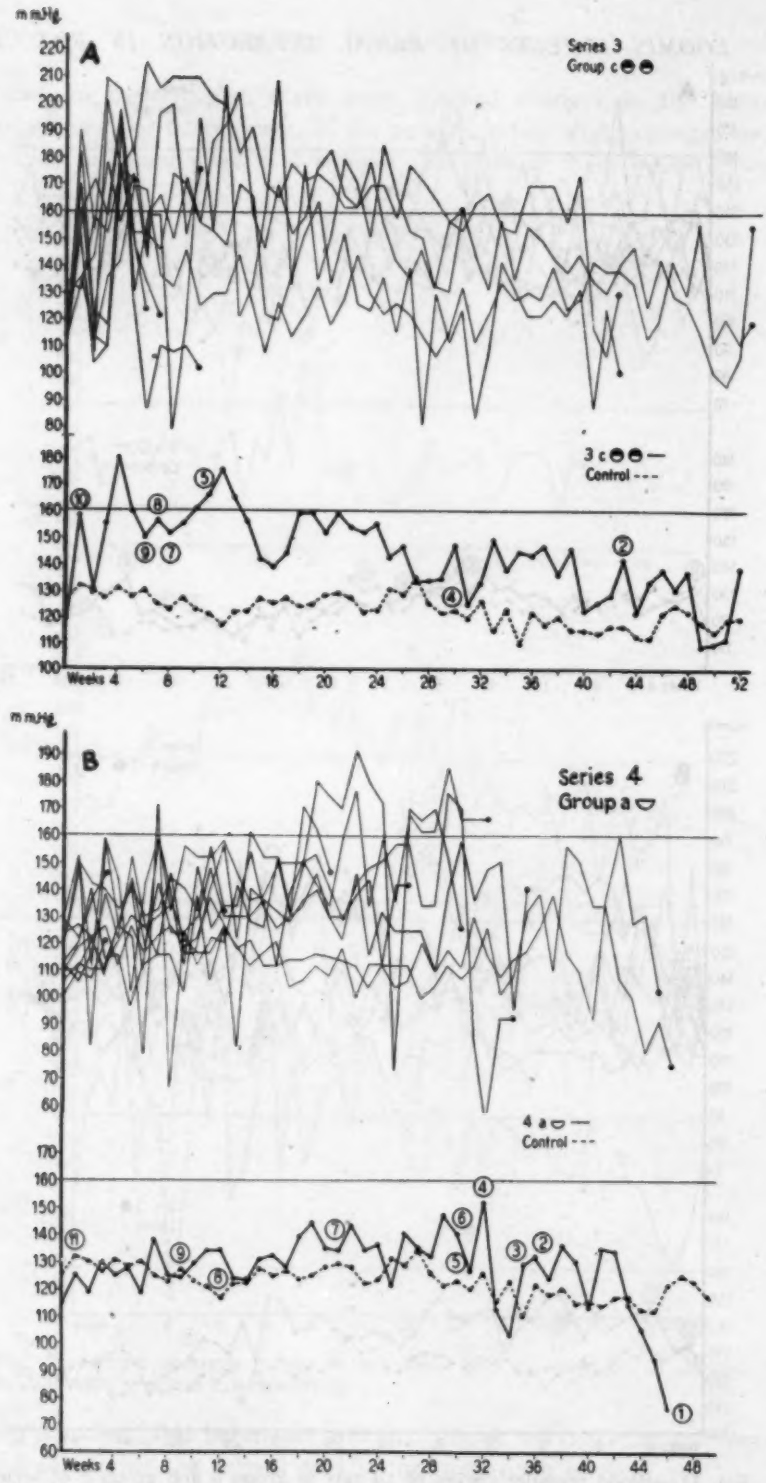

Fig. 12.—Blood pressure curves of all rats in series 3, group *c*, and series 4, group *a*. (See the legend of figure 9 for further explanation.)

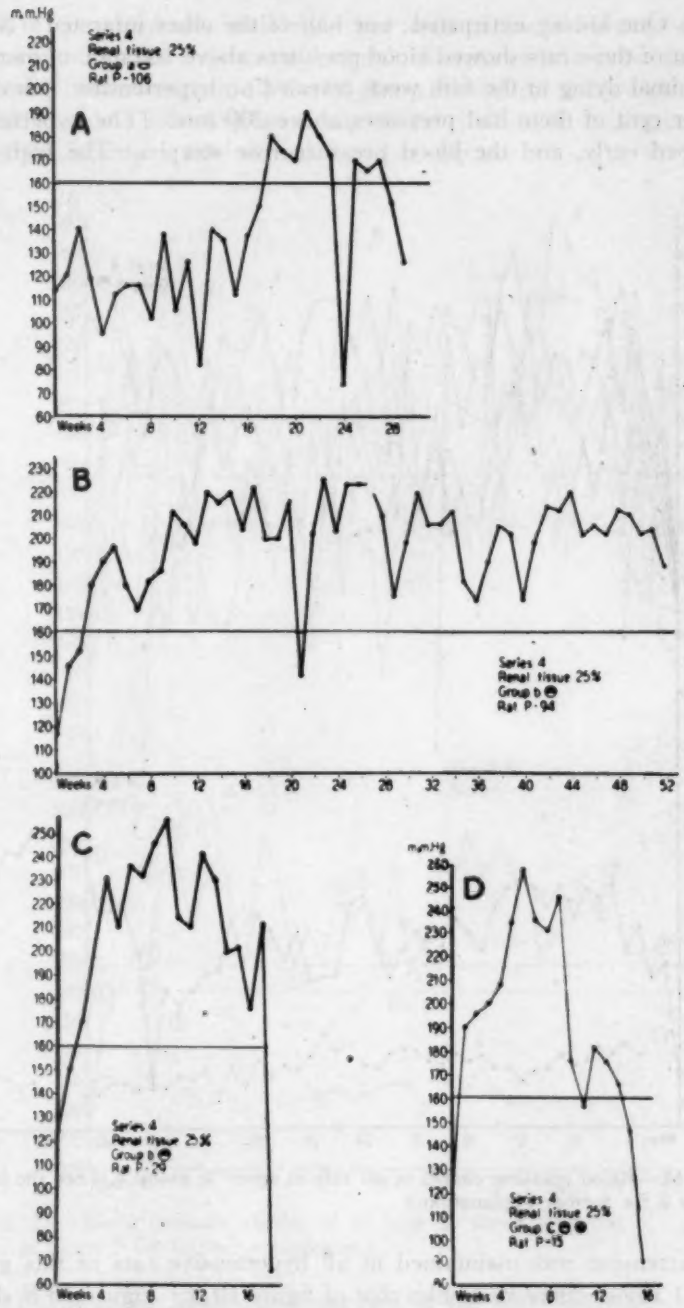

Fig. 13.—Blood pressure curves of individual rats in series 4. *A*, *B*, *C* and *D*, series 4, groups *a*, *b* (represented by 2 rats) and *c*, respectively.

(*b*) One kidney extirpated; one half of the other infarcted: Ninety per cent of these rats showed blood pressures above 160 mm. of mercury. One animal dying in the fifth week revealed no hypertension. Seventy-two per cent of them had pressures above 200 mm. The hypertension developed early, and the blood pressure rose steeply. The high level

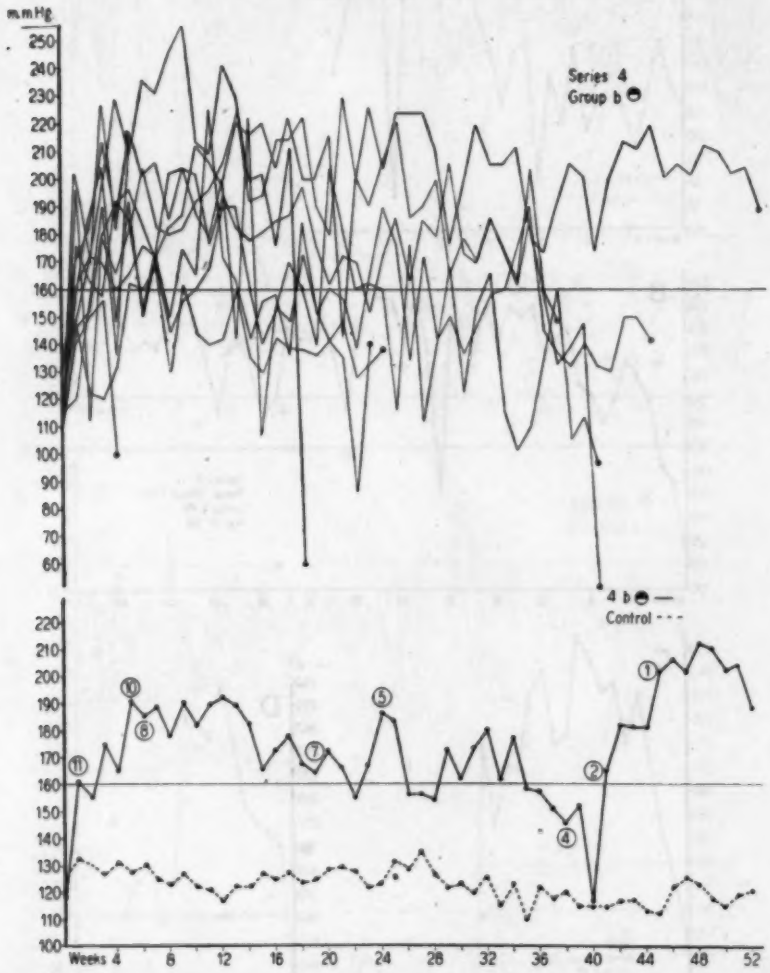

Fig. 14.—Blood pressure curves of all rats in series 4, group *b*. (See the legend of figure 9 for further explanation.)

of hypertension was maintained in all hypertensive rats of this group except 1 whose curve resembles that of figure 10 *B*. Figure 13 *B* shows the weekly pressures of a rat throughout one year, while figure 13 *C* shows those of a rat dying at eighteen weeks. All the individual and the mean curves are shown in figure 14. Arterial lesions were found

in all of these animals and in 54 per cent of them were severe and extensive. Besides hypertrophy, renal changes of the type shown in figure 6 *C* were found in all of the group except the rat which died in the fifth week. Fifty-four per cent of the 11 rats in this group died before six months. One animal survived one year.

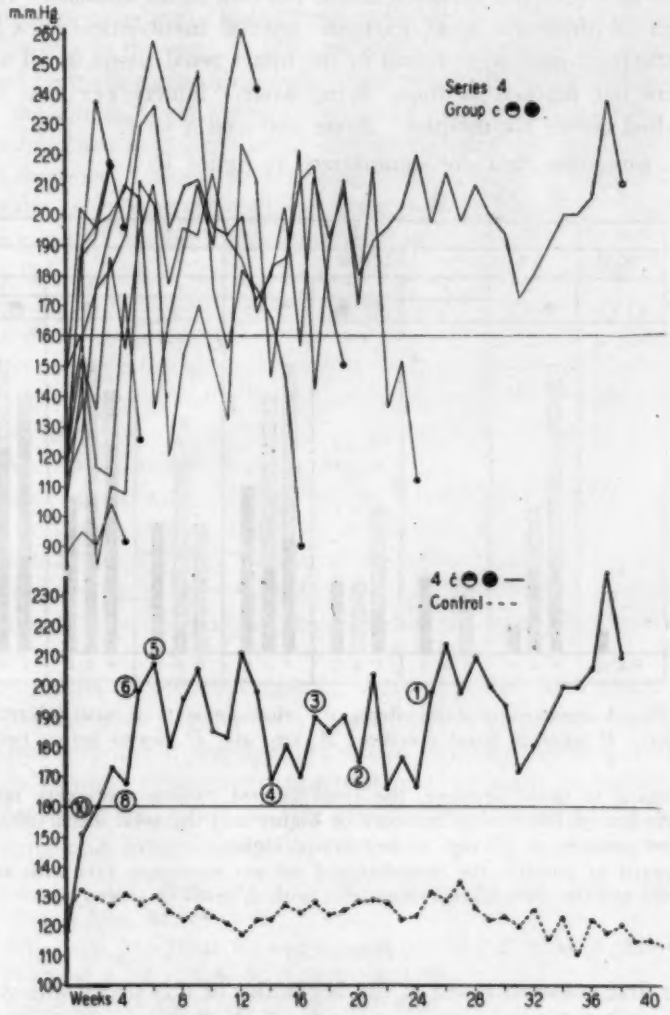

Fig. 15.—Blood pressure curves of all rats in series 4, group *c*. (See the legend of figure 9 for further explanation.)

(*c*) One entire kidney and one half of the other infarcted: In this group the blood pressure rose above 160 mm. of mercury in 90 per cent of the animals and above 200 in 80 per cent. One animal showing no hypertension died in the fifth week. Elevation of pressure appeared

in 70 per cent of the animals in the first week. The blood pressure curves were similar to those of group *b*. (In fig. 13 compare *D* with *C* and *B*). All the individual and the mean curves are shown in figure 15. The 1 rat which lived more than six months had sustained hypertension until death at thirty-eight weeks. The arterial lesions in this group were severe and occurred in 100 per cent of the animals. Seventy per cent of these rats had extreme arterial involvement. Changes besides hypertrophy were found in the intact renal tissue of all animals but were not marked in those dying early. Ninety per cent of this group died before six months. None survived a year.

The foregoing data are summarized in figure 16.

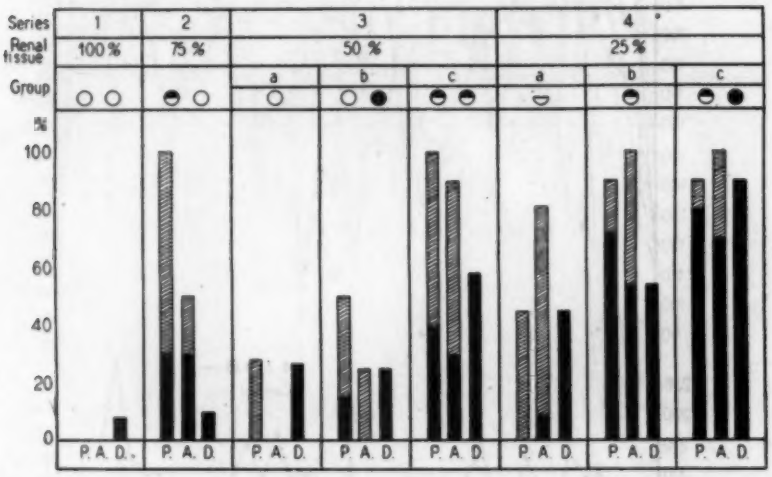

Fig. 16.—A comparison of the effects of various amounts of renal infarction and extirpation. *P* signifies blood pressure; *A*, arteritis; *D*, deaths before twenty-six weeks.

In regard to blood pressure, the cross-hatched column represents rats with blood pressure of 160 mm. of mercury or higher and the solid black column rats with blood pressure of 200 mm. of mercury or higher.

In regard to arteritis, the cross-hatched column represents rats with any type of arteritis and the solid black column rats with arteritis of severe type.

COMMENT

The first question posed at the beginning of this paper was whether or not renal infarction causes hypertension. To a certain extent this had been affirmatively answered by the experimental and clinical observations of a number of workers in the past. Goldblatt [13] summarized the experimental work in this and related fields in 1938. Much of

13. Goldblatt, H., in The Harvey Lectures, 1937-1938, Baltimore, Williams & Wilkins Company, 1938, vol. 33, p. 237.

the early experimental work, of which that done by Cash [14] is the most extended and significant, is confused and inconclusive and has given rise to unfounded conceptions and simplifications, which have in turn influenced later studies. One of these, for example, is that hypertension following infarction, unless it occurs immediately, does not develop at all. Another is that a large amount of tissue must be infarcted for hypertension to occur. Both these concepts have been found by me not to be true of the rat. It is hoped that the results of the experiments reported here clarify to some extent the details of the problem.

In the clinical field the association of renal infarction and hypertension has been frequently noted, but the opinion that they are causally related has been voiced in few instances, a notable exception being the report of a case studied by Prinzmetal, Hiatt and Trageman.[15] Fishberg [16] and Yuille [17] have reported similar cases. The well known case of Boyd and Lewis [18] has been dismissed from consideration as an instance of hypertension due to infarction by some commentators [19] and indeed by the authors of the report themselves, because they thought that changes in renal arterioles might have accounted for the elevation of blood pressure.[20] Yuille [17] has recently reviewed the clinical aspect of these questions in a consideration of the relation of obstructive lesions of the main renal artery to hypertension.

In the present status of the problem, uncertain both from the experimental and from the clinical side, it was felt that a reexamination of this questioned point with the rat as the experimental animal was desirable and timely especially since I had gained a background of anatomic facts from a detailed exploration of infarcted renal tissue by newer methods.[1]

The results of the experimental work reported here establish that renal infarction is a potential cause of hypertension in rats since it elicits this response if the development of hypertension is not hindered by other factors. The same statement may be made in regard to the part played by infarction in the production of vascular lesions of a necrotizing and inflammatory type.

14. Cash, J. R.: Bull. Johns Hopkins Hosp. **35**:168, 1924; Proc. Soc. Exper. Biol. & Med. **23**:609, 1926.

15. Prinzmetal, M.; Hiatt, N., and Trageman, L. J.: J. A. M. A. **118**:44, 1942.

16. Fishberg, A. M.: J. A. M. A. **119**:551, 1942.

17. Yuille, C. L.: Am. J. M. Sc. **207**:394, 1943.

18. Boyd, C. H., and Lewis, L. G.: J. Urol. **39**:627, 1938.

19. Smith, H. W.; Goldring, W., and Chassis, H.: Bull. New York Acad. Med. **19**:449, 1943.

20. If arteriolar changes had been the mechanism in this case, it is unlikely that such alterations would have been unilateral, so that the drop in pressure which occurred on removal of the infarcted kidney would in fact be inexplicable according to their interpretation.

The acute experiments of Winternitz and co-workers,[21a] using the dog, constitute the only work in which there has been a study of these relationships. These workers demonstrated that necrosis of vascular walls occurred after ligation of both renal arteries. They were able to elicit only minimal lesions when the artery to only one kidney was ligated.[21b] In my experiments it has been shown that in the rat necrotizing and inflammatory changes of vascular walls followed infarction of the kidney and occurred not only when there was infarction of considerable tissue but also when 75 per cent of the normal tissue remained intact and there could be no question of renal insufficiency.

Having established by the present investigation that in the rat renal infarction is regularly followed by physiologic and anatomic changes in the vascular system, the query as to whether these effects can be explained by absorption from the infarct can be examined. Certain experiments besides those of Winternitz and his group, just cited, suggest that they can be so explained. For example there are those of Taquini [22] with the dog, and those of Prinzmetal and his collaborators [23] with several species of animals, including the rat, in which the renal artery was completely occluded by a clamp for a period of several hours and in which on release of the clamp elevation of blood pressure occurred. There is also Goldblatt's [24] experiment in the dog in which hypertension failed to follow occlusion of both vein and artery but developed when the artery alone was occluded. Prinzmetal and co-workers [25] observed that in cats extracts of kidneys which had been deprived of their circulation for six hours and the perfusate of a kidney of a human subject [15] with renal embolism yielded a greater amount of potential pressor substance than was found in normal kidneys. In all these experiments there is certainly evidence that can be taken to mean that blood flowing through renal tissue after complete ischemia carried out a substance which acted to elevate blood pressure. If this is so why then is there not hypertension in all cases of renal infarction and why does not the rise in pressure occur shortly after occlusion of the renal vessel?

The reaction of hypertension under these conditions appears to depend on the fulfilment of several requirements, the most obvious of

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21. (*a*) Winternitz, M. C.; Mylon, E.; Waters, L. L., and Katzenstein, R.: Yale J. Biol. & Med. **12**:623, 1940. (*b*) Winternitz, M. C., and Katzenstein, R.: ibid. **13**:15, 1940.

22. Taquini, A. C.: Rev. Soc. argent. de biol. **14**:222, 1938.

23. Lewis, H. A.; Leo, S. D., and Prinzmetal, M.: Am. Heart J. **21**:319, 1941.

24. Goldblatt, H.: Ann. Int. Med. **11**:69, 1937.

25. Leo, S. D.; Prinzmetal, M., and Lewis, H. A.: Am. J. Physiol. **131**:18, 1940.

these being that the pressor substance must gain entrance into the blood stream. If it is present in the injured tissue, in order for enough of it to be absorbed into the blood to be expressed in terms of hypertension, blood needs to flow through the infarct to a sufficient extent that drainage of the injured area is possible. In the Taquini and Prinzmetal experiments cited, such a flow was accomplished simply by removing the clamp from the artery. When, however, a renal artery is ligated, or completely occluded by a thrombus as in human cases, the blood can flow into the infarct from the neighboring renal parenchyma only by way of the narrow intrarenal anastomotic connections of the intertubular network or through pathways even less direct and numerous than these, namely, the extrarenal capillary anastomoses, and against the impediments offered by stasis, edema and clotting. A lapse of time is therefore necessary before the flow is established through a sufficient mass so that the absorption of effective amounts of the hypertensive agent may occur.

If hypertension depends on absorption of the necrotic tissue, it is less likely to develop at all, or it should take longer to do so, in cases in which the establishment of contact between the necrotic tissue and the circulating blood is delayed than in those in which it is more immediate. This is demonstrated in the experiment in which one main renal artery was ligated and severed (group 3 *b*, one kidney showing complete infarction), for in half of these rats hypertension did not develop. In the animals of this group which did exhibit hypertension it developed more slowly than in any other group of rats with infarcted tissue. The mass of necrotic tissue was, however, equal to or more than that in other groups in which hypertension appeared more rapidly and in 100 per cent of the animals (group 2, with infarction of one half of one kidney, and group 3 c, with infarction of one half of each kidney). The obvious difference between these groups is that in group 3 *b* there were not abundant intrarenal anastomoses between the vessels of the injured tissue and the general circulation by which blood could enter directly into the peripheral part of the infarct from the neighboring renal parenchyma. It could, indeed, come into the necrotic mass only by the extrarenal anastomoses between the branches of the renal artery which supply the perirenal fat, the capsule, the ureter and the pelvis, arising proximal and distal to the point of section, and which anastomose outside of and at some distance from the necrotic tissue. The time required for the circulation to be established in the necrotic mass must necessarily, therefore, have been greater in rats with complete infarction of one kidney than in rats with partial infarction of both kidneys. No other explanation seems possible than that the difference in hypertensive reaction is based on the anatomic factors

detailed in the foregoing paragraph, and this leads to the conclusion that the hypertension which follows infarction is due to absorption.[26]

The duration of hypertension also appears to be related to absorption. During the period of revascularization of the infarct, the contact of the necrotic tissue with the blood is increasing, yet the mass of necrotic material is decreasing, so that though an increasingly greater flow is established throughout the tissue, with the passage of time there is progressively less substance to be drained. In an earlier study [1] it was found by dissection that the extension of patent blood vessels throughout the infarct ceased in the second month after infarction. Loss of substance in the infarct, however, continued for an indefinitely longer period. The hypertension, if it is an effect of absorption, should therefore diminish after an interval, and this is what happened in the groups of animals with more than 25 per cent of the renal tissue uninvolved by infarction. The blood pressure declined to considerably lower levels after a period of from three to six months, and sometimes reached a normal figure. Though in some of these rats hypertension persisted until the end of the experiment, in none was the initial high level maintained. The mechanism by which hypertension, even if at lower levels, is thus prolonged after the tissue might presumably be exhausted of its pressor substance will be discussed later.

Can the necrosis and inflammation of the arteries be explained by the assumption that they, too, are due to absorption of products from the infarct? I believe that they can at least partially be explained along the lines of the preceding argument, in spite of the fact that they occur also when a large amount of renal tissue is removed but the kidney is not otherwise injured. The evidence that they are related to absorption from the infarct is found in the fact that in the animals with infarction vascular arterial lesions were exhibited most extensively and most severely when absorption was occurring most rapidly as evidenced by the rapidity of the reduction in size of the necrotic mass. Animals dying in the last twenty-six weeks of the experiment showed in the main no vascular lesions or none that were acute. It was also observed that the group which had structurally the least efficient means for drain-

26. The fact that one rat in each of the groups 4 *b* and 4 *c* did not show hypertension in the four weeks which they lived after infarction does not invalidate this conclusion. These two animals were in poor condition from the time of operation and did not make a proper recovery. Both, however, showed arterial lesions. That the ability to react to the stimulus which raises blood pressure is lacking in sick animals is well recognized clinically, and this weakness may account, according to Fishberg,[16] for the irregularity of hypertension following renal embolism in human beings and for the fall in blood pressure which sometimes occurs in the final days before death in formerly hypertensive persons. The latter is a phenomenon which was often exhibited in these experiments.

age of the infarct, i. e., group 3 *b*, discussed in a foregoing paragraph, showed the fewest and mildest arterial lesions.

As opposed to the factor of absorption, the part played by the reduction of renal tissue in the effects observed after renal infarction must next be considered. Winternitz and associates in their studies [21a] observed that necrotizing vascular lesions occurred in the dog after complete removal of the renal tissue, i. e., bilateral nephrectomy, but that they were much more numerous and severe when both kidneys showed complete renal infarction or when both ureters were ligated. Holman [27] also observed in the dog that vascular lesions occurred following total nephrectomy alone.

It was demonstrated in my experiments that the reduction of the renal tissue to 50 per cent of its original mass does not produce hypertension or arterial lesions while the loss of 75 per cent may result in both these conditions. The vascular injury in the latter instance was, however, in most of the rats minimal, and to locate it required meticulous observation.

As to the hypertension, reduction of renal tissue has been found to produce it in the rat by a number of workers, notably Chanutin and Ferris,[28] Rytand and Dock [29] and Wood and Etheridge.[30] It is difficult or impossible, on the other hand, to cause elevation of blood pressure by this means in the dog.[31] In the experiments reported here, reduction of renal substance to 25 per cent resulted in hypertension after several months in some of the animals. The difference in degree, however, between the hypertension appearing after infarction and that after subtotal nephrectomy indicates that they must be due to different initial mechanisms, for there can be no question of absorption in the latter case.

It is clear, however, that an influence must be ascribed to the factor of loss of renal tissue when the removal of a large amount of tissue (50 per cent) is combined with infarction; for severe arterial lesions, blood pressures persisting at high levels (over 200) and early death of the animals did not result from either procedure alone but from their combination.

The mechanism operating from loss of renal tissue appears to be one by which the activity of an agent affecting the vasculature is enhanced in the milieu created by reduction of normal renal function below a certain critical level. It seems apparent from this, as has been pointed

27. Holman, R. J.: Am. J. Path. **19**:159, 1943.

28. Chanutin, A., and Ferris, E. B.: Arch. Int. Med. **49**:73, 1932.

29. Rytand, D. A., and Dock, W.: Arch. Int. Med. **56**:511, 1935.

30. Wood, E. J., and Etheridge, C.: Proc. Soc. Exper. Biol. & Med. **30**: 1039, 1933.

31. Mason, M. F.; Robinson, C. S., and Blalock, A. J.: J. Exper. Med. **72**: 289, 1940.

out in discussions of the humoral mechanism of renal hypertension,[32] that normal renal tissue can neutralize, modify, destroy or excrete those substances which bring about the vascular changes. The balance of opinion, as far as hypertension is concerned, is that normal renal tissue neutralizes or destroys the pressor substance and does not excrete it. This has been demonstrated in the work of Rodbard and Katz.[33] Certain agents, if present in sufficient quantity in the internal environment created when the amount of normal renal tissue is insufficient for their neutralization, are capable of eliciting the vascular phenomena. These substances may be formed in necrotic renal tissue or in renal tissue functionally deranged and, in the case of total nephrectomy, in the absence of renal tissue.

It is difficult in any particular instance to determine, therefore, which factor, infarction of renal tissue or insufficiency of renal tissue, is of the greater relative importance in the production of the vascular effects. However, in analyzing the results in groups *2*, *3 c* and *4 b* (fig. 16) it is quite evident that the amount of normal renal tissue remaining is more important in determining the degree of anatomic or physiologic change in the vessels than the amount of tissue showing infarction, for with decreasing amounts of renal tissue the disturbances become progressively more pronounced.

It was observed not only that the excision of renal tissue enhanced the effects of infarction on the vascular system but that progressive degenerative changes took place in the remaining renal tissue when the reduction was as high as 75 per cent. These renal changes appear to be of the same sort and degree as those described by some[34] as resulting from subtotal nephrectomy and those found in the dietary experiments of others,[35] in most of which at least one kidney had been removed. The resulting degenerative changes in the glomeruli and the tubules appear to be the result of overloading of the kidney remnant and production of functional strain, as suggested by Wood and Etheridge.[30] Whatever their origin they still further reduce the amount of functioning renal tissue, so that an acceleration of the complete cycle occurs.

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32. Lewis, H. A., and Goldblatt, H.: Bull. New York Acad. Med. **18**:459, 1942. Grollman, A.; Harrison, T. R., and Williams, J. R., in Publication 13, American Association for the Advancement of Science, 1940, p. 274.

33. Rodbard, S., and Katz, L. M.: J. Exper. Med. **73**:357, 1941.

34. Gross, P.; Cooper, F. B., and Morningstar, W. A.: Am. J. Path. **13**:101, 1942. Wood and Etheridge.[30] Pappenheimer, A. M.: J. Exper. Med. **64**:965, 1936.

35. Allen, R. B.; Bollman, J. L., and Mann, F. C.: Arch. Path. **19**:341, 1935. Chanutin, A., and Ludewig, S.: Arch. Int. Med. **58**:60, 1936. Moise, T. S., and Smith, A. H.: Arch. Path. **4**:530, 1927. Newburg, L. H., and Curtis, A. C.: Arch. Int. Med. **42**:801, 1928. Medlar, E. M., and Blatherwick, N. E.: Am. J. Path. **13**:881, 1937.

Another factor contributing to the disturbance of renal function and hypertension may be the renal arterial lesions which, while minimal or absent in most animals in my experiments, were quite extensive in those groups with infarction plus 75 per cent reduction of normal renal tissue.

On the basis of the foregoing considerations, the factors which may interact to effect and enhance the vascular reactions of hypertension and the arterial lesions in these experiments may be summarized as follows:

I. Factors Related to Infarction (Necrosis of Renal Tissue): 1. The extent of the infarct (amount of pressor substance). 2. The degree of revascularization of the necrotic tissue (facility of absorption).

II. Factors Related to the Amount of Renal Tissue Remaining: 3. The degree to which reduction of renal tissue diminishes an agent derived from the living tissue that neutralizes the pressor substance of the infarcted tissue. 4. The degree to which the metabolic overload of the remaining tissue reduces renal function. 5. The extent to which renal vascular lesions progressively reduce renal tissue and function. 6. A factor causing hypertension and vascular lesions which is present as a direct result of excessive reduction of renal substance (75 per cent nephrectomy).

In table 2 each of these hypothetic factors is given a value as it may be estimated from the conditions of the experiments and microscopic evidence. These values are totaled for each experimental group, and the observed results of the experiments are ranged beside them for comparison.

Although there are some discrepancies and the whole structure is suppositious, the order of the assigned values agrees fairly well with the order of the magnitudes of the observed results.

The observations made in these experiments seem, therefore, to point to the conclusion that necrotic renal tissue is a source and reservoir for an agent, or agents, which when absorbed into the blood can cause hypertension and necrotizing inflammatory lesions of the arteries. It may only be conjectured whether there are a number of agents effecting these conditions, whether the action is direct or mediated and whether the agents are the same as the humoral elements which are responsible for the results obtained when the hemodynamics of living renal tissue are altered by constricting the renal artery.

One objection that might be raised to this hypothesis is that the hypertension from infarction in these experiments was too protracted to be due to a substance lasting for so long a time in necrotic tissue, and the opinion might be held that some further added mechanism is implicated which would bring about a renewal of the effective substance. Such a mechanism might be a reduction due to the restrictive effect of the scar of the infarct on the pulse pressure in the unaffected portion of the kidney, especially the tissue which survives at the border of the infarct. This

explanation might be valid were it not for those experiments in which hypertension developed following complete infarction of the whole kidney, in which there was no living tissue. Moreover, there is scar tissue at the site of the removal of the poles in three-quarter nephrectomized animals without renal infarction, but the effects were different in time of development and in degree from those observed after infarction, as has been shown.

TABLE 2.—*A Comparison Between the Numerical Evaluation of Hypothetic Factors in the Condition of Each Group and the Observed Results*

	Hypothetic Factors *							Results				
	1	2	3	4	5	6		7		8		9
Group	Extent of Infarct Amount of Pressor Substance	Blood Supply to Infarct Facility for Absorption	Loss of Renal Tissue with Consequent Loss of Neutralization Factor	Loss of Renal Function Due to Damage of Remaining Tissue by Overload	Loss of Renal Tissue from Vascular Damage	Direct Factor Present as a Result of 75% Reduction of Renal Substance with No Infarct	Total Numerical Value*	Blood Pressure Above: 160 Mm.Hg	Blood Pressure Above: 200 Mm.Hg.	Arterial Lesions: Any Type	Arterial Lesions: Severe Type	Dead Before 26 Weeks
4c ◓ ●	+++	++000	+++	++	++	+	16	90	80	100	70	90
4b ◓	+	++0	+++	++	++	+	12	90	72	100	54	54
3c ◓ ◓	++	++0++0	++	0	+	0	11	100	40	90	30	60
2 ◓ ○	+	++0	+	0	+	0	6	100	30	50	30	10
2b ● ○	++	00	++	0	0	0	6	50	16	25	0	25
4a ◡	0	0	0	++	+	+	4	45	0	81	9	45
2a ○	0	0	0	0	0	0	0	27	0	0	0	27
1 ○○	0	0	0	0	0	0	0	0	0	0	0	8

*Each + is assigned a numerical value of 1

Column 1 - amount of necrotic renal tissue; Each + represents infarction of one half of one kidney.
Column 2 - blood supply to infarct: ++ signifies a supply from peripheral uninjured tissue; 0, a supply from extrarenal connections.
Column 3 - loss of renal tissue and therefore of neutralization factor; Each + represents reduction of neutralization of products of infarction by loss of half of one kidney.
Column 4 - degenerative changes in remnant of kidney according to microscopic evidence: ++ severe; + mild; 0 none.
Column 5 - changes in remnant of kidney due to vascular damage according to microscopic evidence: ++ marked; + minimal; 0 none.
Column 6 - influence of 75 per cent reduction of renal substance alone.

The persistence of renal hypertension after the removal of its apparent source has been observed and discussed by several workers. Kempf and Page [4] stated that hypertension caused by cellophane perinephritis of one kidney can be made to disappear by removal of that kidney if the condition has not been of too long duration. Wilson and Byrom [7] also found persistence of hypertension after removal of the kidney which had had its artery constricted. They explained this persistence by vascular changes occurring in the other kidney as a result of the "vascular crises" of hypertensive animals. Friedman, Jarmon and Klemperer,[8] similarly observed that hypertension remained after the treated kidney was removed and, believing that vascular lesions in the other kidney did not fully account for this persistence, suggested the possible participation of some extrarenal mechanism.

Reed, Saperstein, Southland and Ogden [36] proposed a nervous mechanism.

A possible explanation for the persistence of the hypertension after the supply of pressor substance in the necrotic mass might presumably be exhausted is that an initial substance, absorbed from the infarct, so sensitizes the vessels that the response to other or similar substances, entering the blood in minute amounts as a result of normal metabolism, becomes greatly exaggerated. This idea has been explored by Page [37] as regards renin and angiotonin. He observed that hypertensive animals were slightly sensitive to renin but not to angiotonin and concluded that in such animals there is an increase in renin activator and not hypersensitivity of the blood vesssels.

The histologic appearance of the vascular lesions seen in the present study suggests a sensitizing mechanism of a hyperergic nature. The lesions are histologically identical with those produced in rats and rabbits with such substances as antikidney serum,[38] bacterial vaccines,[39] horse serum [40] and pig renin [41] and are also similar to the lesions observed by Clark and Kaplan [42] and by Rich [43] in patients to whom serum and sulfonamide compounds had been administered. Certainly these lesions, appearing as they do in the absence of hypertension, cannot be explained as due to the fluctuation between high and low pressures as proposed by Wilson and Byrom.[7] They are also found in the absence of renal failure, which Goldblatt [44] held was a necessary condition to their production.

And finally, it must also be kept in mind that there may be one unifying underlying principle at the root of the similar vascular reactions which appear either in response to a wide variety of experimental procedures or naturally.[45] As suggested by Selye and Pentz,[46] there may be participation of the adrenal cortical hormone or there may be some general colloid disturbance such as Hueper [45b] has

36. Reed, R. K.; Saperstein, L. A.; Southland, F. D., and Ogden, E.: Am. J. Physiol. **141**:709, 1944.

37. Page, I. H.: Am. J. Physiol. **134**:789, 1941.

38. Masugi, M., and Sato, Y.: Virchows Arch. f. path. Anat. **293**:615, 1934.

39. Metz, W.: Beitr. z. path. Anat. u. z. allg. Path. **88**:18, 1936.

40. Rich, T., and Gregory, J. E.: Bull. Johns Hopkins Hosp. **72**:65, 1943.

41. Leiter, L., and Eichelberger, L.: J. Clin. Investigation **22**:11, 1943.

42. Clark, E., and Kaplan, B. I.: Arch. Path. **24**:458, 1937.

43. Rich, T.: Bull. Johns Hopkins Hosp. **71**:123, 1942.

44. Goldblatt, H.: J. Exper. Med. **67**:809, 1938.

45. (*a*) Rackemann, F. M.: Arch. Int. Med. **73**:248, 1944. (*b*) Hueper, W. C.: Arch. Path. **38**:162, 245 and 350, 1944; **39**:51, 117 and 187, 1945. (*c*) Smith and others.[90]

46. Selye, H., and Pentz, E. I.: Canad. M. A. J. **49**:264, 1943.

held responsible for inflammatory vascular reactions with fibrinoid necrosis. Such a "plasmatic" colloid disturbance related to the degree of dispersion of interacting colloid particles might arise in the allergic state. The puzzling fact that so many investigators have produced similar results by such diverse means seems to lead to the conclusion that a multiplicity of measures results in identical necrotizing and inflammatory lesions. This suggests that the underlying mechanism must be a basic change occurring when the parts of a constellation fall into place, a constellation whose structure is such that in one of its parts diverse entities can substitute one for another without altering the effective pattern. It is obvious that having reached this stage of speculative hypothesis the elucidation of this subject must await considerable further factual contribution.

SUMMARY

Infarction of the kidney of the rat is followed by hypertension and by necrotizing and inflammatory arterial lesions.

Partial infarction of one kidney was followed more promptly by hypertension than was total infarction of one kidney. Total infarction of one kidney, in fact, did not produce hypertension in 50 per cent of the animals tested. The foregoing observations may be explained by the difference in the anatomic relations of the anastomosing blood vessels in the 2 cases.

The conclusion is drawn that the necrotic renal tissue is the source of vasopressor and necrotizing agents which are absorbed into the blood stream.

The hypothesis is offered that the vessels become so sensitized to these substances that the vascular reactions, both structural and functional, to these or other, similar substances entering the blood in minimal amounts as a result of normal metabolism become exaggerated and prolonged.

The amount of active renal tissue remaining has an influence in modifying the effects of infarction.

AN ANALYSIS OF THE KLIPPEL-FEIL SYNDROME

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IN 1912 Klippel and Feil described the pathologic anatomy of absence of the neck in a 46 year old man.[1] The anatomic basis of the syndrome since known by their names consists essentially in a congenital fusion and numerical reduction of the cervical vertebrae. Since the original description of this rare condition, most of the communications have been reports of clinical cases of a less extreme type. The three characteristic clinical features of the syndrome are shortness of the neck, limitation of movement of the head and lowering of the hair line.

In the present paper I shall discuss a theoretic interpretation of the anatomic basis of the syndrome and its relation to Sprengel's deformity and to certain neurologic disorders and consider a possible mechanism whereby such compound defects may take place. A new clinical case is recorded.

REPORT OF A CASE

The patient is a girl of 10 years; her neck appears short and broad, and the free edge of the trapezius muscle passes directly from the occiput to the lateral end of the clavicle and gives the neck a webbed appearance (figs. 1 and 2). There is marked limitation of the movement of the head in all directions particularly of lateral bending. The hair line is lower than normal. With the exception of a deformity of the second upper right molar tooth, the teeth are normal. The uvula is bifid. A minor degree of bimanual synkinesia and a slight defect of hearing of the right ear are present.

The roentgenograms reveal in the whole cervical portion of the spinal column a malformation which consists of a synostosis from the second cervical to the first thoracic vertebra and is accompanied by marked shortening (figs. 3 and 4). The posterior arch of the atlas is fused to the laminas and the spine of the axis, and the succeeding four cervical spines are also fused together. Several of the transverse processes are similarly affected. It is possible that there is a cleft in the neural arches of the first two vertebrae. The articulation between the atlas and the occipital condyles is free. There are apparently six vertebral segments which appear compressed and widened, especially in the upper half of the column. It is difficult to identify the individual bodies of the vertebrae, and the number of segments is suggested by the number of intervertebral foramens, which are clearly shown. Bilateral cervical rib is present.

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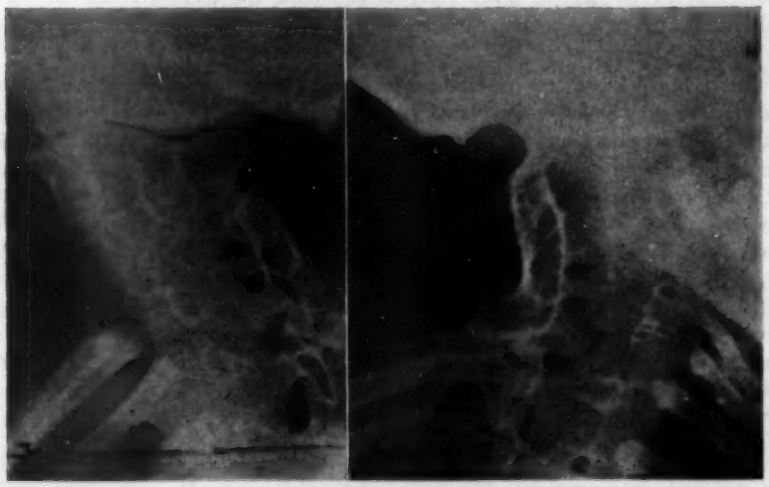
1. Klippel and Feil, A.: Bull. et mém. Soc. anat. de Paris **87**:185, 1912; Nouv. iconog. de la Salpêtrière **25**:223, 1912; Bull. et mém. Soc. d'anthrop. de Paris **3**:101, 1912.

Figs. 1 and 2.—The width and the shortness of the neck, are shown, in contrast to the slender build of the patient.



Figs. 3 and 4.—The roentgenograms illustrate the shortening, the synostosis and the irregularity of the cervical region. Indications of the individual segments are apparent, as shown by the presence of the intervertebral foramens.

PATHOLOGIC ANATOMY

Postmortem studies of the Klippel-Feil syndrome are rare. There is a small number of descriptions of anatomic specimens in which the osseous deformity only is considered. In the original description of an extreme example the cervical vertebrae were considered to be absent, the fused cervical mass consisting of the upper four thoracic vertebrae. In the 2 cases described by Mitchell,[2] the atlas was fused to the occiput, and the intervertebral disks were irregular or obliterated. In other cases the vertebrae are fused either throughout or in the lower cervical region only, or the fusion may involve the upper three or four thoracic vertebrae. The bodies have been found to be ossifying from two widely separated centers, and the anterior wall of the vertebral canal may be several times its normal width. In the probable cases of Fairbank[3] and those of Laignel-Lavastine and Miget[4] the number of cervical vertebrae seemed to be four. The same number of very deformed and noticeably widened vertebrae appeared in the roentgenogram in a case observed by Crouzon and Liège.[5] Feller and Sternberg[6] expressed the belief that the number of segments can be determined by counting the transverse processes and remarked that a numerical reduction cannot be confirmed.

Spina bifida is frequently found. According to Mitchell,[2] it is of a false type, as some of the laminas curve down to meet in the midline in a fused mass in the lower cervical region, so that a triangular opening is formed, with the apex directed downward and the base toward the occiput. The triangular deficiency in the arches is covered by a layer of fibrous tissue, and occasionally it extends to the upper thoracic region. The occipital bone may be closely approximated to the defect (Feller and Sternberg[6]) and this approximation appears to be related to the cervical lordosis. As a rule, there is no meningocele. An exception is seen in the case of Latto,[7] who commented on the presence of a meningocele in the region of the occiput. Feller and Sternberg[6] observed in 1 of their cases that the hindbrain region was displaced into the upper part of the vertebral canal and noted that this displacement was similar to that found in the Arnold-Chiari malformation.

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2. Mitchell, H. S.: Arch. Dis. Childhood **9**:213, 1934.
3. Fairbank, H. A. T.: Brit. J. Surg. **1**:553, 1914.
4. Laignel-Lavastine, M. M., and Miget, A.: Rev. neurol. **1**:782, 1930.
5. Crouzon, O., and Liège, R.: Bull. et mém. Soc. méd. d. hôp. de Paris **52**:917, 1928.
6. Feller, A., and Sternberg, H.: Virchows Arch. f. path. Anat. **285**:112, 1932.
7. Latto, D.: Brit. M. J. **1**:669, 1942.

Jarcho and Levin [8] reported that sections of the spinal cord revealed normal structure. On the other hand, Avery and Rentfro [9] stated that in their case sections of the upper part of the spinal cord showed it to be almost divided into two parts by a deep anterior fissure, that lower sections revealed two anterior fissures and that some sections showed doubling of the central canal and gliosis of a moderate degree.

Fusion and deformities of the ribs occur (Ingelrans and Piquet [10]), and cervical ribs are often present. In cases of the Klippel-Feil syndrome with associated high scapula, the latter is smaller than normal, the infraspinous parts being relatively more affected, and so it resembles the normal fetal scapula in the relation between the vertical and the transverse diameter. A bar of cartilage or bone or a band of fibrous tissue may attach the vertebral border of the scapula to the lamina of a cervical vertebra. Areas of embryonic myoblastic tissue were found throughout the aplastic muscles in a 6 week infant dissected by Middleton.[11]

Other abnormalities occur, some of which clearly depend on the primary cervical lesion, such as torticollis, facial asymmetry, lowered nipple line, kyphosis and thoracic scoliosis, the last occasionally due to a hemivertebra. Also described are abnormal dentition (Willard and Nicholson [12]), cleft palate (Nobel and Frawley [13]), micrognathia (Demeler [14]), hydrocephalus (Feller and Sternberg [6]), strabismus (Thomson [15]), platybasia (Furst and Ostrum,[16] Merio and Risak [17]), pulmonary stenosis (Bizarro [18]), patent foramen ovale and interventricular septum (Mitchell [2]).

ETIOLOGY

The consensus regarding the cause of the Klippel-Feil syndrome is that it is a disorder of segmentation. Views of the cause and the pathogenesis vary. They include dysplastic factors resulting in inhibition or necrosis of chrondrogenic centers of the vertebrae (Jarcho and Levin [8]), morbid conditions of the parent (Rechtman and Horwitz [19]),

8. Jarcho, S., and Levin, P. M.: Bull. Johns Hopkins Hosp. **62**:216, 1938.
9. Avery, L. W., and Rentfro, C. C.: Arch. Neurol. & Psychiat. **36**:1068, 1936.
10. Ingelrans, P., and Piquet, J.: Rev. d'orthop. **15**:297, 1928.
11. Middleton, D. S.: Edinburgh M. J. **41**:401, 1934.
12. Willard, DeF. P., and Nicholson, J. T.: Ann. Surg. **99**:561, 1934.
13. Nobel, T. P., and Frawley, J. M.: Ann. Surg. **82**:728, 1925.
14. Demeler, W.: Ueber familiäre missbildungender Wirbelsäule, Inaug. Dissert., Münster, 1933.
15. Thomson, J.: Arch. Dis. Childhood **12**:127, 1937.
16. Furst, W., and Ostrum, H. W.: Am. J. Roentgenol. **47**:588, 1942.
17. Merio, P., and Risak, E.: Ztschr. f. klin. Med. **126**: 455, 1934.
18. Bizarro, A. H.: Lancet **2**:828, 1938.
19. Rechtman, A. M., and Horwitz, M. T.: Am. J. Roentgenol. **43**:66, 1940.

sequelae of infections of infancy or of intrauterine life (Rebierre [20]), weakening of the hereditary powers in the parent (Nobel and Frawley [13]) and injurious influences resulting in inhibition of regressive or progressive processes during development (Foggie [21]); in some cases the syndrome is regarded as syphilitic in origin (Roger, Arnaud and Audier [22]). Occasionally the numerical reduction of the vertebrae, spina bifida or a defect in the intervertebral disks is considered to be the primary factor in the malformation. Kallius [23] based a classification of the anomalies of the vertebral axis on the theory of Rosenberg, which relates the inconstant morphologic character of the human vertebral column to its phylogenetic development and probable future forms and suggests that the deformities can be explained by stability or instability of structure. This theory is considered by Kallius to be more satisfactory than a theory based on the assumption of accidental disturbances of the chromosomal determinants.

It has been stated that the Klippel-Feil syndrome is not hereditary or familial (Nobel and Frawley [13]) even by those (Thomson [15]) who have pointed out the cases (cited by Feil [24]) in which the syndrome was observed in father and son and in mother and 3 children (cited by Sicard and Lermoyez [25]); occasionally cited is a case reported by Kallius,[23] in which the syndrome occurred in father and daughter. To these may be added a probable case reported by Sick [26] in which a sister of the patient's father and other relatives on the father's side were affected, the cases of Jarcho and Levin [8] in which a brother and a sister were involved, with a minor vertebral defect in the mother, the cases of Demeler [14] in which at least 2 brothers and 1 sister showed the syndrome, those of Clemmensen [27] in which the patients were mother and daughter, and 1 of Bizzaro's [18] in which the father and the mother were both affected, as well as a probable case reported by Bar [28] in which brother and sister were the patients. Hangarter and Dieker [29] reported the case of a female with the Klippel-Feil syndrome whose sister, both parents and other relations showed skeletal defects. When the cases in which no apparent hereditary or familial element was shown are considered, the constancy of the deformity

20. Rebierre, P.: Presse méd. **31**:452, 1923.

21. Foggie, W. E.: Edinburgh M. J. **42**:421, 1935.

22. Roger, H.; Arnaud, M., and Audier, M.: Marseille-méd. **1**:233, 1934.

23. Kallius, H. U.: Arch. f. orthop. u. Unfall-Chir. **29**:440, 1931; **31**:287, 1932.

24. Feil, A.: L'absence et la diminution des vertèbres cervicals, Thesis, Paris, no. 212, 1919.

25. Sicard, J. A., and Lermoyez, J.: Rev. neurol. **30**:71, 1923.

26. Sick, P.: Deutsche Ztschr. f. Chir. **67**:556, 1902.

27. Clemmensen, V.: Acta radiol. **17**:480, 1936.

28. Bar, P.: Bull. Soc. d'obst. de Paris **6**:425, 1903; **7**:250, 1904.

29. Hangarter, W., and Dieker, W.: Ztschr. f. menschl. Vererb.- u. Konstitutionslehre **21**:236, 1937.

observed suggests a genetic basis. It may be added that Neuhof [30] and more recently Schwarzweller [31] gave evidence of a hereditofamilial incidence of the closely related Sprengel deformity.

There is also general agreement that the incidence is equal in males and females (Bauman [32]; Foggie [21]; Willard and Nicholson [12]), though some (Nobel and Frawley [13]) have stated that it is more common in males. However, if only those cases which appear to be genuine examples of the Klippel-Feil syndrome and which present closely similar anatomic features are selected, it appears that there is a preponderance of females; though the total number of cases is small, this preponderance is probably significant. In such a selection of 52 cases in the literature there are 34 females and 18 males. This higher incidence in females is supported by the observation of Gilmour.[33]

Some authors require a numerical reduction of the vertebral axis to complete the syndrome, but many cases are classified as instances of Klippel-Feil syndrome without numerical reduction and in others its presence is difficult to prove (Mitchell [2]). Reduction occurred in only 1 of the 6 cases of Feller and Sternberg.[6] They regarded the reduction in this case as physiologic. But it seems that reduction is present more frequently than can be accounted for on physiologic grounds. In a study of 1,420 vertebral columns LeDouble [34] observed only 2 in which the number of cervical vertebrae was reduced to six. Avery and Rentfro [9] expressed the view that numerical reduction is an essential part of the syndrome, and at the same time they agreed with Müller [35] that it occurs when the growth of the normally developing parts forces the misplaced and abnormal parts into a mass formation as the body grows older. Reduction of the segments in the cases classified as Sprengel's deformity has been reported by Critchley,[36] Niederle,[37] Fairbank [3] and others. Many cases which some authors would consider to be instances of the Klippel-Feil syndrome are classified by others as cases of Sprengel's deformity. Further examples are described under still other headings (Sever [38]). Heidecker [39] pointed out the difficulty of distinguishing the two conditions when Sprengel's deformity is bilateral. A well known

30. Neuhof, H.: Am. J. Dis. Child. **7**:357, 1914.

31. Schwarzweller, F.: Ztschr. f. menschl. Vererb.- u. Konstitutionslehre **20**: 350, 1937.

32. Bauman, G. I.: J. A. M. A. **98**:129, 1932.

33. Gilmour, J. R.: J. Path. & Bact. **53**:117, 1941.

34. LeDouble, A.-F.: Gaz. méd. du centre **17**:29, 1912.

35. Müller, W.: Deutsche Ztschr. f. Chir. **242**:94, 1933.

36. Critchley, M.: Brit. J. Surg. **14**:243, 1926.

37. Niederle, B.: Časop. lék. česk. **63**:1743, 1924; cited by Du Toit.[41]

38. Sever, J. W.: Boston M. & S. J. **186**:799, 1922.

39. Heidecker, H.: Beitr. z. klin. Chir. **144**:303, 1928.

early clinical case of the Klippel-Feil syndrome is that of Clarke,[40] and the probable cases of Bar [28] and Sick [26] have been mentioned. A cervical osseous deformity which now would probably be classified by many as the Klippel-Feil syndrome was described by Rokitansky in 1850. Du Toit [41] remarked that cases of high scapulas were reported by Underburg in 1693, and doubtless other early cases could be found which modern authors would place in one of the two categories. Böhm [42] expressed the opinion that the Klippel-Feil syndrome is not an entity and claimed priority for a description of the cervical malformation published in 1909. These factors make it difficult to assess the exact number of cases described, the total ranging from 50 to a recent estimate of 133 made by Rechtman and Horwitz [19]. A large proportion especially of the earlier cases are described in the French literature (Feil [24]; Dubreuil-Chambardel [43]; Lance [44]; Michel and Nicolleau [45]; Crouzon and Martin,[46] and others).

Though Feller and Sternberg [6] regarded nervous defects as rare, it will be observed that in addition to the pathologic anatomy already described, other disorders found are mental weakness and deaf-mutism (Foggie [21]; Bauman [32]), nystagmus (Latto [7]), late spastic paralysis (Guy-Laroche and Klotz [47]; Baruch [48]), late syringobulbia and syringomyelia (Kallius [23]; Critchley [36]; Du Toit [41]), central facial weakness (Furst and Ostrum [16]), bimanual synkinesia (Bauman [32]; Willard and Nicholson [12]) and late involvement of the sympathetic nervous system (Turner, Shoulders and Scott [49]). Rebierre [20] described a case in which he found partial anesthesia of the soft palate, right lingual hemiatrophy, a zone of cutaneous anesthesia at the base of the neck and paralysis of the right vocal cord. Owing to the rarity of bimanual synkinesia alone and the rather frequent association with the Klippel-Feil syndrome, it is stated (Bauman [32]) that synkinesia should be regarded as part of the syndrome, but Willard and Nicholson [12] considered that the two are independent.

It is clear from a review of the cases in the literature that their most constant features are synostosis, flattening of the vertebrae, narrowing or obliteration of the intervertebral disks, shortening of the cervical spine

40. Clarke, J. J.: Lancet **2**:1350, 1906.
41. Du Toit, F.: Brain **54**:421, 1931.
42. Böhm, M.: Zentralbl. f. Chir. **58**:2019, 1931.
43. Dubreuil-Chambardel, L.: Presse méd. **29**:353, 1921.
44. Lance, M.: Presse méd. **29**:27, 1921.
45. Michel, A., and Nicolleau: Marseille-méd. **59**:394, 1922.
46. Crouzon, O., and Martin, R.: Rev. neurol. **1**:270, 1923.
47. Guy-Laroche and Klotz, B.: Rev. neurol. **2**:47, 1933.
48. Baruch, R.: Ztschr. f. d. ges. Neurol. u. Psychiat. **139**:462, 1932.
49. Turner, E. L.; Shoulders, H. S., and Scott, L. D.: Am. J. Roentgenol. **40**:43, 1938.

and spina bifida. In at least some cases it appears that the characteristically lowered hair line is due to the same type of hirsutism as that found in other regions in spina bifida occulta, as has been noted by Rebierre.[20] Reduction occurs but it is probably less common than the roentgenograms suggest, and it is doubtful if it is an essential part of the disorder. It is also clear that the variations seen in the syndrome are chiefly those of degree.

COMMENT

The pinciple of gastrulation, according to which the germ layers are formed, is common to all vertebrates, though the mechanisms may differ. These mechanisms, dynamic processes involving coordinated cellular movements, have been studied in those forms in which gastrulation takes place in a manner similar to that of gastrulation in man. The position of the materials which normally will become the somites, myotomes and other structures has been mapped in considerable detail (Pasteels[50] and others), following the application by Vogt of the method of vital staining, by colored marks. The position of the areas varies somewhat in different creatures which possess a disklike form in early stages, as man, though in gastrulation the essential feature is the relative movements which take place rather than the form of the map.

Let it be assumed that a disturbing factor is present over the area where the rostral end of the primitive streak appears. Whether or not the streak represents a part of gastrulation, such a factor would involve approximately the prechordal plate, the rostral end of the notochord, the cervical somitic mesoblast and the mesoblast of the head and neck region from which the myotonic muscles of the neck and other structures are developed. That is, it would affect the earliest structures to be involved in gastrulation. Such a factor may arise on fertilization and could become established even before the first division of the egg. Environmental factors acting very soon after fertilization and before cleavage have been shown to produce localized defects in Heteroclitus (Hinrichs and Genther[51]); these defects were produced by ultraviolet rays acting for a short period and the results varied in type; the effect on axial structures in such cases is generally manifested by a tendency toward duplication.

In this connection it may be added that duplication of the cervical spine in the Klippel-Feil deformity cannot be excluded; the roentgenograms in certain cases resemble those of a partial duplication. Feller and Sternberg[6] described a fetus in which sections of the malformed part of the vertebral column showed that the remainder of the notochord was divided into two parts. In experimental animals, doubling of this

50. Pasteels, J.: Arch. Biol. **47**:205, 1936.
51. Hinrichs, M. A., and Genther, I. T.: Physiol. Zool. **4**:461, 1931.

structure is followed by vertebral duplication. Some cases of the Klippel-Feil syndrome may represent a primary duplication of the axis with subsequent incomplete reunion. Early experimental findings have shown that if the mesodermal axis is duplicated, the neural organ is subject to the same change by a process of induction. Thus in this connection the finding of Avery and Rentfro [9] acquires special significance; in their case the spinal cord presented a doubling of the central canal and other features suggesting duplication.

Gabriel [52] has shown experimentally that environmental conditions (in this case variations in temperature) resulted in numerical variations in the somites. A lowered temperature produced an actual increase in the number of somites; a raised temperature decreased the number. The reduction tends to occur at the caudal end of the axis and is related to the amount of material available for somite formation and to the speed of the developmental reactions. Differentiation and growth can be independent of each other. If the former becomes precocious relative to the somite separation and growth, fusion of segments as well as numerical reduction may occur. It is pointed out that as mesodermal cells become differentiated they may lose their ability to become separated into somites. Thus an acceleration of differentiation can result in fusion of segments. A generalized influence as far as the segments are concerned produces an effect similar to that which occurs in the Klippel-Feil syndrome, namely, fusion and reduction in their number. It might be suggested that an increase in the temperature of the environment of the embryo would have the same effect. An increase in temperature is usually followed by raised metabolic activity. If this is the basis of the anomalies of segmentation, a genetic factor which raises metabolic activity in a similar manner could produce a similar result. It appears that, though the reduction and the fusion are due to distinct immediate causes, they are associated under a generalized influence. Feller and Sternberg [6] have suggested that it is not a true fusion but a disorder associated with a defect in the disks. Partsch [53] expressed the belief that the disorder arises when the vertebral column is represented by a cartilaginous bar. The latter condition, however, is not present at any time during development. Though too close an analogy between man and Heteroclitus should not be drawn, the principle may well be similar; the experimental production in the Axolotl of complex malformations involving deficiencies and reductions similar to those of genetic origin in man is described by Brandt.[54] But the Klippel-Feil syndrome often involves more than fusion and a numerical reduction of segments. An

52. Gabriel, M. L.: J. Exper. Zool. **95**:105, 1944.
53. Partsch, F.: Arch. f. orthop.- u. Unfall-Chir. **24**:199, 1927.
54. Brandt, W.: J. Exper. Biol. **20**:117, 1944.

explanation is required for the selective locality of the abnormality at the cranial end of the axis as well as for the frequently associated high scapula and muscle defects. It appears that the disturbance occurs at a specific time or over a specific area. In this case it is possible that fusion may be independent of the numerical reduction. Thus it seems that such a mechanism as an alteration of the temperature of the environment or a general effect exercised on metabolism by a genetic factor cannot account for all cases of the syndrome. The extent and the position of the disturbance in the Klippel-Feil deformity may be explained if one assumes a factor whose action is local, even if the action is a nonspecific one, such as an acceleration in the developmental rate. A factor acting in time, that is during the gastrulation process for the cervical structures, could produce a similar result. In either case there is a certain specificity in space or time; this specificity implies a genetic factor. Points in favor of the temporal conception will be discussed below and are obtained from the consideration of the relationship between the Klippel-Feil syndrome and Sprengel's deformity.

The appearance of the effects of the early disturbance may be placed shortly after gastrulation, that is with the appearance of the somites rather than with that of the definitive vertebrae. This is suggested by those cases in which the vertebral bodies are wide and possess bilateral ossification centers such as might result from arrest in development with ossification in the bilateral chondrification centers. At the same time it would appear that the spina bifida is at least partly mechanical. If the arches, which ossify some time before the bodies, were to differentiate in contact with each other because of the lack of depth in the bodies, fusion might be assumed. Subsequent differential growth in the bodies could account for the type of spina bifida which is described.

There is clearly a relation between congenital high scapula, or so-called Sprengel's deformity, and the Klippel-Feil syndrome, as the former usually appears in association with a cervical malformation similar to that found in the latter. The converse is however not always true. Lichtenstein [55] in a discussion of observations reported by Gustafson and Oldberg suggested that platybasia is a connecting link between the two anomalies. Some authors (Bizarro [18]) suggested that the Klippel-Feil syndrome is an advanced stage of Sprengel's deformity, but this appears to imply not only that there is a direct relationship of a progressive nature between the two conditions but that the Klippel-Feil syndrome is always accompanied by Sprengel's deformity. This does not appear to be so, and, further, the degree of severity of the one is not necessarily accompanied by a corresponding degree of severity of the other. The

55. Lichtenstein, in discussion on Gustafson, W. A., and Oldberg, E.: Arch. Neurol. & Psychiat. **54**:1184, 1940; cited by Furst and Ostrum.

relation seems rather to be one of common origin. The tissues of the scapular region and those of the cervical vertebrae are developed to some extent from a common mesodermal substratum, although they are not differentiated simultaneously. A disturbance producing the Klippel-Feil syndrome may have ceased to act by the time the scapular structures appear, with the result that a pure Klippel-Feil syndrome is produced. A similar type of disturbance occurring later might affect the developing scapular structures and produce Sprengel's deformity. If at the same time it affects the axis, the latter would have passed the stage at which the typical Klippel-Feil syndrome could be produced. This hypothesis accounts for the peculiar relationship between the two conditions. A similar connection may exist between the Klippel-Feil deformity and iniencephaly. Gilmour [33] stated that the latter is a more severe form of the deformity seen in the Klippel-Feil syndrome. In support of this belief that the two conditions are the same, Gilmour cited as examples of iniencephaly 3 cases classified by Feller and Sternberg [6] as examples of the Klippel-Feil syndrome. There is to be found in both infants and adults a number of severe forms of the Klippel-Feil syndrome which do not possess the characters of iniencephaly; notable among them is the original form described by Klippel and Feil.[1] It is agreed that certain cases described by Feller and Sternberg may be instances of iniencephaly and that the latter may have the characters of the Klippel-Feil deformity in the cervical region but that the converse does not apply.

With regard to the teeth and the mouth Schröder [56] remarked on the association of cleft palate and malformations of the spinal column which is observed in certain families. It was noted in the case reported earlier in this article that there was a minor defect related to cleft palate, that is, a bifid uvula. Platt [57] showed that the tissue underlying the oral region is partly composed of material of neural crest origin, and the suggestion is made that it may be the source of the primitive dentine. This mesectoderm material migrates from the dorsal region of the neural tube to the buccal region. A disturbance of the mesoderm of the head region might have the effect of arresting some part of this material. Thus the cleft palate may well be the result of the branchial arch structures of the palate growing into oral ground tissue which is defective. Failure of eruption or malformations of the teeth may also be correlated indirectly with the same early mesodermal disorder.

There does not seem to be a description of the pathologic anatomy of the ears in those cases of the Klippel-Feil syndrome with deaf-mutism, though a deformity of the ear in the form of absence of the external meatus is described by Ingelrans and Piquet.[10] When congenital deaf-

56. Schröder, C. H.: Beitr. z. klin. Chir. **169**:402, 1939.
57. Platt, J. B.: Morphol. Jahrb. **25**:377, 1897.

mutism is the chief defect, its pathologic character varies. Schiebe's type comprises more than half the cases. In connection with such auditory defects Bartelemez and Evans [58] described a mesectoderm proliferation from the hindbrain region in man, which probably contributes to the visceral arch mesenchyme. Further, Stone [59] showed experimentally that removal of neural crest material will result in defects of the visceral arch skeleton. Since the auditory ossicles are formed from visceral arch material, it is possible that the factor discussed in connection with the adynamic failure in somitic morphogenesis might be responsible for the retardation of migration of mesectoderm which results in defective differentiation in the middle ear. Such a disturbance in development, if severe, would produce a defect not dissimilar to Siebermann's type of congenital deafness. If the deaf-mutism is sensory and at the same time not coincidental, an explanation might be provided by a consideration of the dependent relation between the otic vesicle and the head mesoderm; that is, the latter takes part in determining the appearance of the former. The presence of the head mesoderm is also responsible for the continued normal development of the otic vesicle (Kaan [60]). Since it has been shown by Mangold [61] that in some vertebrates the removal of certain parts of the mesoderm underlying the cranial end of the neural plate results in cyclopia, the formation of the eyes is also related to the underlying mesoderm; however, in man sensory defects of a character comparable to deaf-mutism, that is, optic aplasia, have not been described in these cases. There is a distinction, however, apart from the species difference, in that the underlying material involved in the induction of the ear may be related to the proximity of those precervical somites which are taken up in the basis cranii. It is admitted that such auditory, dental and palatal defects as those described in connection with the Klippel-Feil syndrome may be coincidental, but the foregoing facts appear to be suggestive.

The association of synkinesia with the syndrome has been mentioned. Baigley [62] remarked that all patients with hemiplegia show it and cited Stewart for the information that it is common to see conjugate movements in spastic hemiplegia, and that they are really tonic reflex reactions similar to those in decerebrate animals; the movements are reflex, due to changes in muscle tone. The type of synkinesia described in the Klippel-Feil syndrome does not appear to be of this type. Willard and Nicholson [12] and others have remarked that every movement of one hand

58. Bartelemez, G. W., and Evans, H. M.: Contrib. Embryol. **17**:1, 1926.
59. Stone, L. S.: J. Exper. Zool. **44**:95, 1926.
60. Kaan, H. W.: J. Exper. Zool. **78**:59, 1938.
61. Mangold, O.: Ergebn. d. Biol. **7**:193, 1931.
62. Baigley, in discussion on Bauman.[32]

is copied almost exactly by the other. Climbing a ladder can be impossible because of the synchronized movements of the hands. Thus it would appear that there is a considerable element of physiologic movement involved. If so, it may be explained on the basis of certain experimental results. The induction and formation of the central nervous system in many vertebrates have been shown to have some dependent relation with the underlying mesoderm during early development. Among these vertebrates mammals may be included, as Töro [63] has shown that neural induction can also occur in this species. By a more refined analysis in suitable cases Holtfreter [64] revealed that there is also a dependent relation of the internal configuration of the spinal cord with the disposition of the immediately surrounding tissues. If in mammals, as well as induction, there is also a similar relation with the disposition of surrounding tissues, the synkinesia may in this manner be related to the primary disorders responsible for the defects in the mesodermal structures. Such disorders of internal configuration as incomplete bilateral segregation of the cells of origin of the brachial plexus might be considered.

CONCLUSIONS

From the example of the Klippel-Feil syndrome presented and from the case reported in the literature it is concluded that the essential features of the cervical deformity are synostosis of two or more cervical vertebrae and flattening and widening of the vertebral bodies. A numerical reduction of the vertebrae is an incidental rather than an essential part of the disorder, as is spina bifida. The latter depends largely on the degree of abnormality of the vertebral bodies. There is evidence that the anomaly has a genetic basis. A number of pathologic conditions which have been found in association with the osseous deformity of the syndrome receive an explanation in the light of recent observations in the field of experimental embryology.

63. Töro, E.: J. Exper. Zoöl. **79**:213, 1938.
64. Holtfreter, J.: Arch. f. exper. Zellforsch. **15**:281, 1934.

OVARIAN INVOLVEMENT IN HODGKIN'S DISEASE

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THE infrequency of ovarian involvement in the course of Hodgkin's disease is apparent from a brief perusal of the voluminous literature of this disease. No mention of such occurrence was noted in any of several standard textbooks of general, surgical and gynecologic pathology. In numerous reports of unusual ovarian tumors no instance of Hodgkin's disease was encountered. A closely related lesion was reported in the first 50 cases filed with the Ovarian Tumor Registry of the American Gynecological Society.[1] A 16 year old patient (case 28) had lymphosarcoma of the ovary secondary to intestinal lymphosarcoma. The accompanying photomicrograph reveals an infiltration strikingly similar in its general characteristics to that of our cases. Reviews dealing with Hodgkin's disease and reports representing relatively large series of cases, as a rule, do not refer to the ovary. In Wallhauser's [2] review ovarian involvement is mentioned without specific reference to the authors cited (Wallthard and Mousson). Similarly, Fabian [3] credited Herard with a report of ovarian involvement but failed to include this author in his bibliography. Over a thousand references are represented in the two preceding reviews. Jackson and Parker,[4] reporting the autopsy observations of 112 cases of Hodgkin's disease, mentioned involvement of the ovary in 2 cases. In one case the involvement was microscopic in character; in the other (tabulated) the extent of involvement was not indicated. Gemmell [5] in a report based on a study of 57 cases of Hodgkin's disease of the female theorized that ovarian hypofunction may be responsible for the occurrence of the disease in women; he described no lesions of the ovary to substantiate this concept, which was based chiefly on the history of reduced or suppressed menstruation in several cases.

That the infiltration of the ovary in Hodgkin's disease can be of considerable extent is illustrated in the cases reported in the following

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From the Department of Pathology, University of Pittsburgh, and Presbyterian and Woman's Hospitals.

1. Novak, E.: Am. J. Obst. & Gynec. **48**:861, 1944.
2. Wallhauser, A.: Arch. Path. **16**:522, 1933.
3. Fabian, E.: Centralbl. f. allg. Path. u. path. Anat. **22**:145, 1911.
4. Jackson, H., Jr., and Parker, F., Jr.: New England J. Med. **231**:35, 1944.
5. Gemmell, A. A.: J. Obst. & Gynaec. Brit. Emp. **30**:373, 1923.

pages. In each case the lesion of the ovary was misinterpreted as a primary tumor from its gross appearance. In case 1, the resident physician who did the autopsy submitted a gross anatomic diagnosis of "carcinoma, probably primary in the ovary, with widespread secondary involvement of the abdominal lymph nodes." Of particular interest is case 2, in which the surgeon, an experienced gynecologist, noted during abdominal exploration an ovarian tumor of such size that it was considered primary in that organ, while the neoplastic enlargement of the mesenteric lymph nodes was considered to be secondary to the ovarian lesion.

REPORT OF CASES

CASE 1.—Mrs. S. G., a 69 year old white woman, was admitted to the Presbyterian Hospital, service of Dr. A. H. Colwell, Dec. 20, 1944. She complained of abdominal pain and a cough of three weeks' duration. In the previous six months she had lost 30 pounds (13.5 Kg.) in weight.

Examination revealed a poorly nourished patient with evidence of vitamin deficiency. None of the superficial lymph nodes were enlarged. The chest was essentially normal. The abdomen was distended and showed evidence of free fluid. An indefinite mass was noted in the epigastrium. The temperature on admission was 102 F., and during the following six days elevation was intermittent, sometimes reaching 103 F. Signs of pulmonary consolidation developed, and after one week of treatment with sulfamerazine her temperature returned to normal. She was unable to take food, became progressively weaker and died Jan. 9, 1945.

Laboratory studies gave results that were essentially normal except for moderate anemia. The blood counts on several occasions revealed the number of red blood cells to vary between 3,070,000 and 3,650,000 per cubic millimeter; the hemoglobin content ranged from 63 to 73 per cent; the white blood cells, from 5,200 to 12,900 per cubic millimeter. Differential examination of the blood films revealed mature polymorphonuclear leukocytes to constitute from 89 to 94 per cent, lymphocytes from 6 to 10 per cent and monocytes from 0 to 1 per cent.

Autopsy (six hours after death).—The body showed evidence of extreme malnutrition. There was no enlargement of any of the superficial lymph nodes. The breasts were atrophic, and the bony thorax was poorly developed. The abdomen was slightly distended, and a poorly defined mass was palpable in the epigastrium. Removal and section of the thoracic organs showed no significant gross abnormalities except for moderately intense pulmonary congestion and edema and small, patchy bronchopneumonic areas in both lungs.

There was 400 cc. of clear ascitic fluid in the peritoneal cavity. Throughout the omentum and the mesentery were numerous prominent lymph nodes, varying from 2 to 5 cm. in diameter. Their cut surfaces were pale, translucent, glistening, fleshy in appearance and studded with small irregular yellow areas of necrosis. The consistency was soft. A large, irregular, coarsely nodular retroperitoneal mass extended from the inferior surface of the diaphragm to the aortic bifurcation. On section numerous lymph nodes were noted, which were firmly adherent to one another and which formed the entire mass. The individual nodes were readily identified and measured from 1 cm. to several centimeters in diameter. Their cut surfaces were similar to those of the mesenteric group. The capsules of all nodes appeared intact, and diffuse interstitial infiltration was not evident. The

pericholecystic and peripancreatic nodes were similarly but less extensively altered. With the exception of the left ovary the abdominal viscera were not noteworthy. There was moderate dilatation of the renal pelves and of the upper portions of the ureters, both of which were incorporated in the retroperitoneal mass.

The uterus, both fallopian tubes and the right ovary showed advanced involutionary atrophy, the ovary measuring 1.5 cm. in its greatest diameter. It was approximately the size and the shape of a shelled peanut. The left ovary was enlarged in an irregular fashion and measured 4.5 cm. in its greatest diameter. It was located in a normal position and was freely movable, and no enlarged lymph nodes were in close proximity. Its surface was smooth, the capsule tense and its contour irregularly oval. The consistency was moderately soft, and on section a well circumscribed irregular nodular mass measuring 4 by 2 by 2 cm. was noted, replacing the bulk of the stroma, remnants of which were compressed laterally. The cut surface of the tissue was pale and fleshy in appearance, similar to that of the abdominal lymph nodes (fig. 1 *A*).

Microscopic Examination.—Sections of the retroperitoneal mass and of the mesenteric, omental, peripancreatic and pericholecystic lymph nodes revealed a similar picture throughout. A highly cellular process had destroyed the nodal structure, only isolated remnants of which remained. The cells were closely spaced and exhibited no structural pattern. In areas, mature lymphocytes were generously intermingled with the tumor. The tumor cells showed considerable pleomorphism. Most of the cells were large and showed much variation in shape. The cytoplasm was abundant, homogeneous and free of granules (fig. 1 *B*). For the most part, it stained intensely acidophilic, but amphoteric and lightly basophilic forms were noted. The nuclei for the most part were large, vesicular and often multilobulated. Prominent nucleoli were frequent. Multinucleated giant cells of the Sternberg-Reed type were commonly encountered.[5a] Mitotic figures were numerous. Smaller forms with single delicate vesicular or pyknotic nuclei and pale-staining cytoplasm were common. Many of the tumor cells were within the sinusoidal spaces, but interstitial infiltration was a prominent feature of the reaction. There were large areas of ischemic necrosis; elsewhere, widespread interstitial fibrosis was present.

Sections of ovary revealed two types of lesions. One was similar to that of the abdominal lymph nodes, consisting of large cells of reticuloendothelial type showing scattered mitotic figures and considerable pleomorphism, in which giant cells of the Sternberg-Reed type were prominent. Clusters of these cells were occasionally noted within the lumens of veins.

In other areas the parenchyma was extensively infiltrated and largely replaced by a heavy lymphoid infiltration, associated at times with moderate interstitial fibrosis. The cells were uniform in size, shape and appearance and were typical mature lymphocytes with scant cytoplasm (fig. 1 *C*). In these areas reticuloendothelial cells were rarely evident. Intermingling of the sarcomatous and lymphoid patterns was noted at the junction of these patterns (fig. 1 *D*). In areas, stroma of ovarian type containing corpora albicantia served to identify the tissue as ovary.

Lymphoid infiltrations similar to that seen in the ovary were noted in sections of lung, pancreas, epicardium, fallopian tube, serosa of small intestine, kidneys and bone marrow. The infiltration of these organs was purely lymphocytic and of only microscopic proportions, rarely replacing parenchymatous tissue.

5a. The inaccuracy of the eponym "Sternberg-Reed" has been recently pointed out by Symmers (J.A.M.A. **128**:1248 [Aug. 25] 1945).

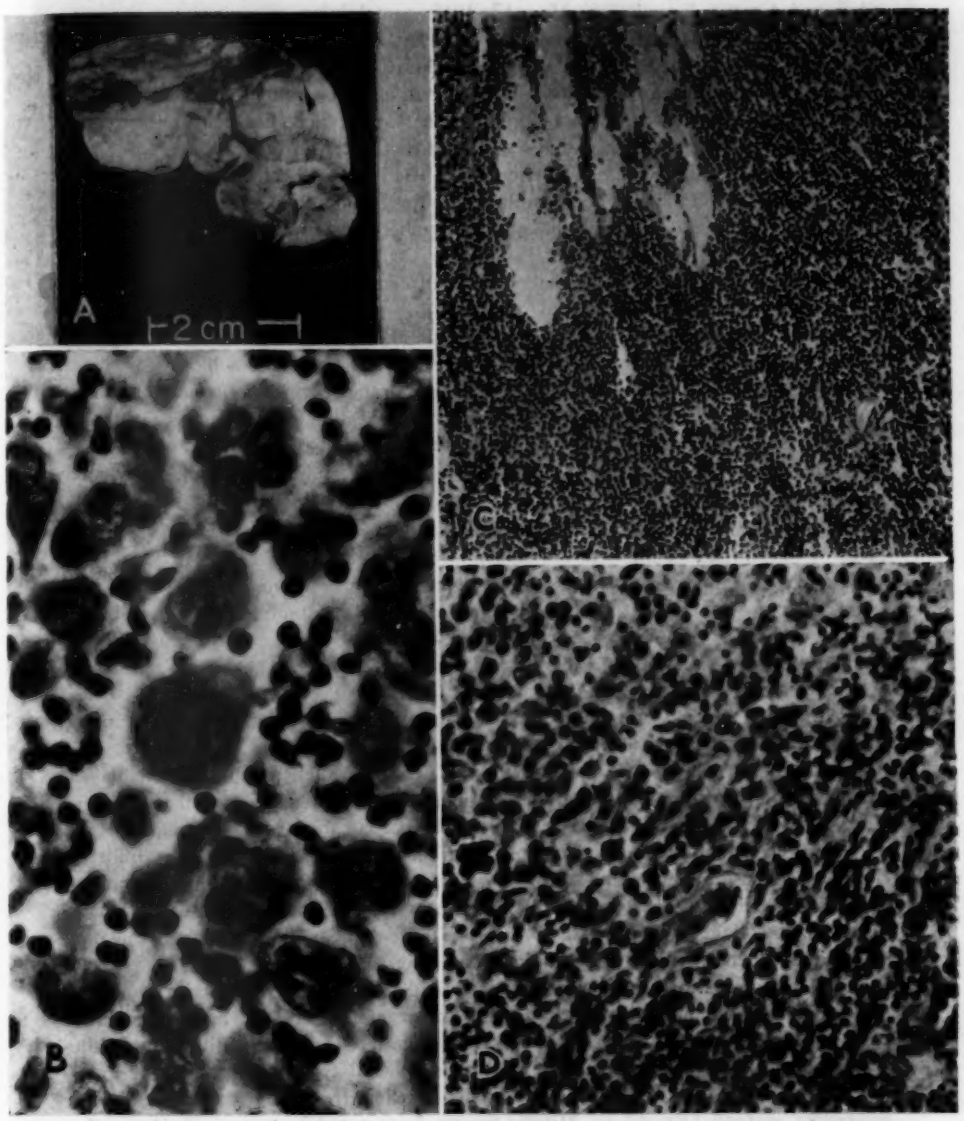

Fig. 1 (case 1).—*A*, ovarian tumor. The cut surface is pale, solid and coarsely lobulated. Displaced ovarian parenchyma appears above.

B, lymph node. The large frequently multinucleated sarcomatous cells are infiltrating the lymphoid parenchyma. × 800.

C, ovarian tumor. There is diffuse lymphoid infiltration around remnants of a corpus fibrosum. × 130.

D, ovarian tumor. The area represents the transition zone between the sarcomatous and the lymphoid infiltration, the latter appearing below. × 290.

CASE 2.—Mrs. V. V., a 35 year old white woman, reported to the Pittsburgh Skin and Cancer Foundation, May 17, 1945, complaining of continuous pressure and cramplike pains in the right lower quadrant of the abdomen, and progressive enlargement of the abdomen of six weeks' duration. On abdominal examination a firm, nontender, orange size mass, dull to percussion, was found in the epigastrium. Pelvic examination revealed an irregular firm nodular mass located in the region of the right ovary. Similar nodules were felt in the cul-de-sac.

Laboratory studies were noncontributory. The red blood cells numbered between 3,520,000 and 3,780,000 per cubic millimeter; the hemoglobin content ranged from 70 to 76 per cent, and the white blood cells numbered from 7,250 to 9,600 per cubic millimeter.

The clinical impression was that of ovarian cancer with metastatic involvement of the abdominal lymph nodes.

The patient was admitted to Woman's Hospital, service of Dr. Alfred A. Pachel, for laparotomy, which was done on June 4. The right ovary and a biopsy specimen of the omentum were removed. A large, solid, orange size mesenteric mass, firm in consistency and fixed on all sides, was noted in the epigastrium. The postoperative surgical diagnosis was primary solid carcinoma of the ovary with secondary involvement of the abdominal lymph nodes. The patient was discharged on the sixteenth postoperative day, following an uneventful postoperative course.

Pathologic Examination.—The specimen consisted of an ovary and an irregular piece of omentum.

The ovary was greatly enlarged, measuring 8 by 5 by 4 cm. It was ovoid and covered by an intact thin capsule which was smooth, glistening, opaque, and discolored in areas by irregular subcapsular hemorrhages. The surface was slightly nodular. On section a pale, yellowish white, moderately firm, fleshy-appearing, solid tissue was noted, of uniform character throughout (fig. 2 *A*).

Within the omental fat were small irregular nodular areas of tissue similar in appearance to that of the ovary.

Sections revealed a thin fibrous capsule, beneath which atrophic remnants of ovarian stroma were noted, containing distinct but often distorted graafian follicles. The parenchymatous and the stromal elements had been largely replaced by a heavy cellular infiltration associated with considerable fibrosis. The infiltration was diffuse, intense and without structural pattern. The fibrosis was of irregular distribution, in some areas extensive and diffuse and productive of heavy depositis of collagen. Elsewhere it was less extensive and disposed as elongated trabeculae which traversed the cellular areas (fig. 2 *B*).

The predominating cells were of lymphoid type, the great majority being typical mature lymphocytes tightly packed in large numbers. Lymphatic nodules with germinal centers were not observed. Scattered diffusely throughout the lymphoid tissue were larger cells of reticuloendothelial type, with acidophilic cytoplasm and large oval or lobulated vesicular nuclei, frequently containing large, prominent nucleoli (fig. 2 *C*). Mitotic figures were noted in several of these cells. Infrequently, double or trinucleated forms were identified, measuring up to 15 microns in diameter. Larger forms were not encountered.

In areas, particularly where fibrosis was prominent, eosinophilic leukocytes were commonly noted, as many as 8 per high power field (objective, 4 mm.; ocular, × 10). The fibrosis and the eosinophilic and lymphoid infiltration combined to impart a distinct granulomatous appearance to these areas.

A similar infiltration was noted in the omentum.

The diagnosis submitted was lymphoblastoma of the ovary and the omentum, probably Hodgkin's type, with a notation that in all probability the involvement

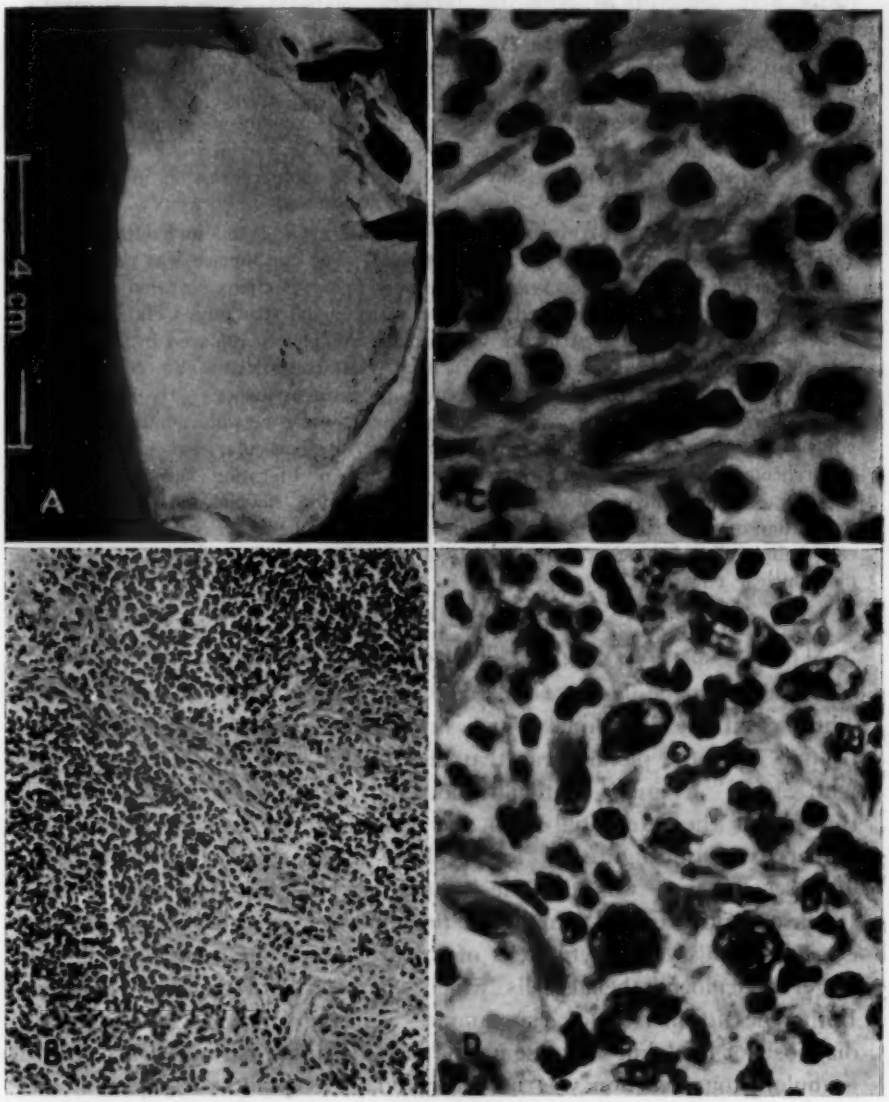

Fig. 2 (case 2).—*A*, ovarian tumor. The cut surface is pale, solid and homogeneous. The ovarian capsule covering the right surface is prominently displayed. Compressed ovarian parenchyma containing two cysts appears at the right upper pole.

B, ovarian tumor. The granulomatous appearance is evident. × 130.

C, ovarian tumor. At the center is a large cell of the Sternberg-Reed type, with two prominent nucleoli. Numerous lymphocytes appear in the field. × 1,000.

D, lymph node. Pleomorphism and fibrosis are distinct. In the central area there are three cells of the Sternberg-Reed type, one showing nuclear lobulation. × 800.

of the ovary was secondary to a process primary in the abdominal lymph nodes. Following and presumably as a result of this report a discrete bean size subcutaneous nodule was detected in the right arm, overlying the area of the insertion of the deltoid muscle.

The patient was readmitted for excision of the subcutaneous nodule on July 17. In the meantime irradiation of the abdominal nodes had been instituted, and over a period of several weeks they showed considerable regression in size and were no longer palpable.

The specimen consisted of an oval encapsulated mass 2 cm. in length, to the surface of which small tags of fat were attached. The cut surface was pale, solid and glistening. The consistency was moderately firm. Sections revealed a lymph node showing moderately advanced alteration of the nodal structure. The germinal centers and the interstitial structure were almost completely replaced by a diffuse lymphoid infiltrate possessing no structural characteristics. The cells were relatively mature and tightly packed within a delicate connective tissue stroma. Scattered in small numbers throughout the pulp were reticuloendothelial cells possessing large oval or lobulated nuclei, generally vesicular but occasionally hyperchromatic and in mitotic division. Stromal proliferation had resulted in considerable thickening and lamination of the capsule, beyond which lymphoid infiltration of the perinodal fat was evident. In the peripheral areas larger reticuloendothelial cells of the Sternberg-Reed type were numerous. They were generally mononuclear (fig. 8).

COMMENT

The diagnosis of Hodgkin's disease in the 2 cases requires discussion.

In case 1 the lesions of Hodgkin's disease were of two types. Throughout the abdominal lymph nodes, which were regarded as the primary site, the picture was that of Hodgkin's sarcoma (Karsner [6]), with large irregular reticuloendothelial cells spreading diffusely throughout the interstitial pulp and sinusoidal spaces and exhibiting numerous mitotic figures. Pleomorphism was particularly pronounced. The second type was that designated as Hodgkin's paragranuloma (Jackson and Parker [4]), in which the infiltrate consisted of masses of closely spaced lymphocytic cells of mature type, containing few of the larger reticuloendothelial cells which characterize Hodgkin's disease. Both types formed the ovarian tumor. Exception may be taken to the diagnosis of Hodgkin's disease in this case inasmuch as the characteristic granulomatous reaction was not observed. Acceptance or rejection of the diagnosis depends entirely on one's opinion as to the necessary diagnostic criteria. If one accepts the broader concept of Hodgkin's disease as one with a variable pattern, subject to mutations and transition in which the tumor changes into the sarcomatous and almost pure lymphoid variants, which have been repeatedly described (Karsner; Ewing [7]; Jackson and Parker; Fabian, and others), the diagnosis in

6. Karsner, H. T.: Arch. Int. Med. 6:175, 1910.

7. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940, pp. 413-415.

this case becomes tenable. Special attention is directed to a study recently published by Herbut, Miller and Erf [8] which illustrates such variability of the histologic pattern in Hodgkin's disease.

In case 2 the ovarian infiltration was obviously lymphoid in character and not consistent with the pattern of any tumor primary in that organ. The occurrence of the larger cells of reticuloendothelial type, resembling poorly developed Sternberg-Reed cells, the scattered eosinophils and the fibrosis led to a diagnosis of lymphoblastoma, probably Hodgkin's disease. The reaction subsequently noted in the lymph node from the arm appeared to substantiate fully the original diagnosis.

That the ovarian involvement in both cases was not the result of fusion with, and direct extension from, contiguous lymph nodes was manifested by the fact that the organs were freely movable, in normal position, unattached to neighboring nodes and each surrounded by an intact ovarian capsule.

The identification of sarcomatous cells within the lumens of veins within the substance of the ovary in case 1 probably serves to explain the genesis of the infiltration in this organ.

SUMMARY

In 2 cases of Hodgkin's disease with unusual involvement of the ovary the gross appearance of the lesion was such that it was misinterpreted as a primary ovarian neoplasm.

8. Herbut, P. A; Miller, F. R., and Erf, L. A.: Am. J. Path. **21**:233, 1945.

PLASMODIUM FALCIPARUM MALARIA

The Coronary and Myocardial Lesions Observed at Autopsy in Two Cases of Acute Fulminating P. Falciparum Infection

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THE literature on malaria conveys the impression that the pathologic aspect of this disease is limited to splenomegaly and pigmentation of viscera, with the additional distinguishing feature of plugging of cerebral vessels and miliary necrosis in Plasmodium falciparum infection. Many authors interpret other lesions as caused by toxins liberated by the parasites or as the reaction from the anemia. What is it that predisposes to plugging of cerebral vessels, and why should one not anticipate a similar phenomenon in other vessels?

MacCallum [1] pointed out that coma in P. falciparum infection is not due to the focal necrosis but to the plugging of the cerebral capillaries. The question might be raised whether cerebral manifestations alone are sufficient to explain the sudden deaths of patients. Cecil [2] stated that a guarded prognosis must be held for a patient in coma or stupor with the cerebral type of P. falciparum malaria and that with hemoglobinuria the prognosis is always grave. Dudgeon and Clarke [3] are quoted: "Death from suddenly developed cardiac failure is common in pernicious forms of subtertian malaria and is due to the severe toxic fatty degeneration of the myocardium." Manson [4] reported gangrene of the toes; he pointed out that the defective nutrition, the edema of the ankles and the dilatation of the ventricles are due to anemia. Strong [5] mentioned fatty degeneration of the heart. Gaskill [6] reported the presence of parasites among and within the cardiac cells. Manson [4] included

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1. MacCallum, W. G.: Textbook of Pathology, ed. 7, Philadelphia, W. B. Saunders Company, 1940, p. 834.

2. Cecil, R. L.: Textbook of Medicine, ed. 6, Philadelphia, W. B. Saunders Company, 1943, p. 437.

3. Dudgeon and Clarke, cited by Strong,[5] p. 77.

4. Manson-Bahr, P. H.: Manson's Tropical Diseases, ed. 11, Baltimore, Williams & Wilkins Company, 1942, p. 71.

5. Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, ed. 7, Philadelphia, The Blakiston Company, 1944, vol. 1, p. 57.

6. Gaskill, cited by Strong,[5] p. 58.

cardialgia among the symptoms, and, crediting Dudgeon and Clarke,[3] attributed low blood pressure to thrombosis of vessels of the adrenal glands. Craig and Faust [7] mentioned no myocardial lesions. Most and Meleney [8] recently reported 7 cases of subtertian malaria, including 2 fatal cases, but in only 1 of these did they observe cerebral lesions. They made no reference to other organs.

It is probably an unusual experience to study the lesions of uncomplicated and untreated acute P. falciparum malaria. It might also appear strange that such cases should occur, particularly when the etiologic aspects are so well understood and routines for suppression and treatment so rigidly enforced. The fact remains that in spite of all precautions there will always be cases in which the infection follows a similar course.

The pathologic observations of these 2 cases should be of interest in that the mechanical factors of the cycle followed by the parasites in the blood undoubtedly contributed a great deal to the production of the symptoms and sudden death.

REPORT OF CASES

CASE 1.—A soldier aged 33, who had been on furlough, collapsed on the street in town. On admission to a hospital he was disoriented and could not give a reliable history. A blood smear was positive for P. falciparum, with 30 per cent of the red cells infested. His pulse was weak and rapid (rate, 112 to 140) but regular; the blood pressure was not recorded. The erythrocytes numbered 1,980,000 per cubic millimeter; the leukocytes, 20,600; the hemoglobin content was 47 per cent. The urine was dark brown and contained albumin (3 plus). His temperature did not rise above 101 F. Treatment was promptly instituted, but five hours after admission the patient died in a manner suggestive of embolism.

Autopsy.—The body was well developed and well nourished, with a tinge to the skin suggestive of quinacrine hydrochloride. The visceral cavities contained no free fluid. The heart was dilated, with the greatest transverse diameter 21 cm.; the weight was 400 Gm., and the musculature seemed very flabby, soft and dark. Small petechiae were seen in the epicardium; the coronary orifices, the valves and the endocardial surfaces were without change. The cut surface of the muscle was dark red but showed no evidence of infarction. The lungs were edematous. The spleen was a dark chocolate brown and weighed 570 Gm. The capsule was extremely thin and tense, and cracked readily when the spleen was manipulated. The cut surface also was dark chocolate brown; the pulp was soft and mushy and washed out readily. The stomach contained particles of undigested food, indicating that the man had a period of well-being just before his sudden collapse. The entire intestinal tract appeared normal. The liver was dark brown, dull and pasty, and weighed 2,020 Gm. There was no gross evidence of hemorrhage or necrosis. The kidneys weighed 280 and 300 Gm., respectively. The capsules were thin and tense and stripped with ease. The cut surfaces were reddish brown, and the cortex was sharply demarcated from the medulla. Grossly,

7. Craig, C. F., and Faust, E. C.: Clinical Parasitology, ed. 2, Philadelphia, Lea & Febiger, 1940, p. 204.

8. Most, H., and Meleney, H.: J. A. M. A. **124**:71, 1944.

no hemorrhages were encountered. The brain showed no significant changes. There was not even pigmentation of the parenchyma. Other organs were considered normal.

Microscopic Observations.—(*a*) Heart: The muscle fibers presented a loose texture, and their striations were faint. In some areas the muscle sheaths were intact, but the cytoplasm was translucent, stained poorly and showed a flaky texture. Miliary areas of hemorrhage were also seen but no leukocytic reaction either in the ischemic or in the hemorrhagic areas. The vessels presented the most conspicuous feature; they either bulged or were plugged with parasites and parasitized red cells. Ameboid forms of parasites adhered to the walls of the vessels, and at the bifurcations clumps of ameboid forms plugged the lumens; frequently thrombi formed in these areas. Endothelial cells lining the capillaries were swollen, and some of them had assumed phagocytic function. Red cells containing trophozoites were seen among normal ones in the lumens of capillaries.

(*b*) Liver: The lobules were distinct, and only occasional red cells and parasites were encountered in the sinuses. The Kupffer cells were large and loaded with pigment granules. In the efferent zones the liver cells contained fat globules. There was also a moderate degree of passive congestion. Cloudy swelling was seen throughout.

(*c*) Spleen: The reticulum was engorged with red cells, many of which contained parasites. Large numbers of phagocytic cells contained debris and reddish brown pigment. Polymorphonuclears were relatively scarce. The malpighian bodies were compressed because of congestion. No scarring or hemorrhages were seen. The capsule was thin, and the trabeculations were delicate.

(*d*) Kidney: Except for swelling of the renal epithelial cells, which contained flaky cytoplasm, there were no significant changes. The capillaries throughout the cortex were relatively free from parasites. Toward the pelvis of the kidney the capillaries were engorged with parasitized red cells containing ameboid forms. There were no areas of necrosis.

(*e*) Adrenal Gland: The vascular sinuses were relatively free from parasites. There was no necrosis, and the cortical cells were well preserved.

(*f*) Bone Marrow; Rib: There was no evidence of destruction of the marrow. Except for occasional large macrophages containing pigment, the section showed no variation from the normal. There was no depletion of any of the myelogenous elements.

(*g*) Brain: The meninges had a loose edematous texture. The capillaries were engorged with red cells and parasitized cells. An occasional area of hemorrhage was encountered showing well preserved red cells and disintegration of the brain substance. There was no accumulation of leukocytes or glial cells in the vicinity of the hemorrhages. Parasitic thrombi or plugs were numerous.

(*h*) Lung: The sections showed a moderate degree of edema and marked engorgement of the vessels; many of the capillaries were conspicuous because of the parasitized red cells within. There was no pneumonia.

Case 2.—A moderately obese man, 70 years of age, had been treated at a local dispensary for food poisoning because of indigestion and diarrhea. Six days later he lapsed into a semistupor and was sent to a hospital. On admssion his temperature was 101 F. The pulse was regular and rapid; the rate, 110. Examination of the chest revealed moisture at the base of each lung; the heart was reported normal. The red cell count was 2,800,000; the leukocyte count was 16,500; the hemoglobin content was 50 per cent. A blood smear was positive for P. falciparum, 40 per cent of the cells being infested. The patient became coma

tose; the heart sounds were more distant; the pulse rate rose to 130 and was irregular and thready; the blood pressure was 60 systolic and 40 diastolic. Before transfusion and treatment were instituted, he suddenly became cyanotic and died, six hours after admission.

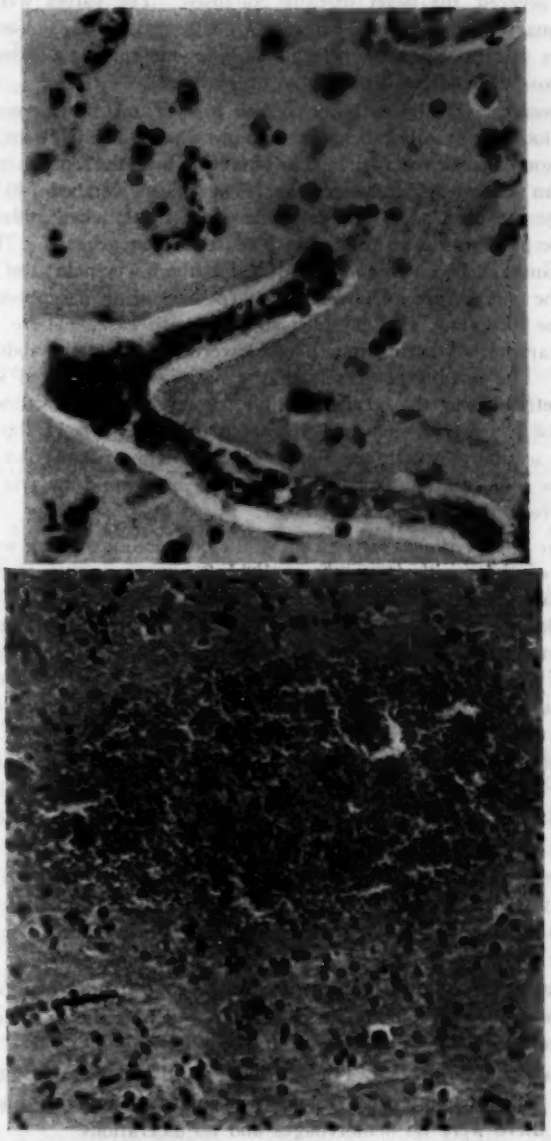

Fig. 1 (case 2).—Branching vessel of the brain, greatly dilated and plugged with ameboid forms of parasites and emboli.

Fig. 2 (case 2).—An area of fresh hemorrhage with cells well preserved and no increase of glial cells. Note capillaries occluded with parasitic emboli.

Autopsy.—The body was that of a moderately obese elderly white man. The visceral cavities were dry. The lungs were free from adhesions, had retracted and were air containing except along the posterior borders, where there was a moderate degree of congestion. The heart was dilated, particularly the auricles; the transverse diameter was 20 cm. The musculature was soft, and when the vessels were severed, the heart literally collapsed. The valves were all normal, and the coronary orifices were patent. On the epicardial surface there were dilated vessels but no scars or petechiae. The cut surface of the myocardium showed no gross evidence of hemorrhage or scarring.

The liver weighed 1,820 Gm., was reddish brown and of firm consistency; the cut surface looked parboiled, being a homogeneous reddish brown, with no evidence of hemorrhage or necrosis. The stomach and the entire intestinal tract were free from ulcerations and petechiae. The spleen weighed 740 Gm. and was dark red. The capsule was as thin as tissue paper and cracked under the slightest pressure. The pulp was soft, mushy, deep red and homogeneous. The left kidney weighed 210 Gm. and had a large cortical cyst at the lower pole; the right weighed 180 Gm. The cut surfaces showed a sharp line of demarcation between the cortex and the medulla. The capsules stripped with ease. There was no gross evidence of scarring. Atheromatous plaques were limited to the abdominal portion of the aorta. The meningeal vessels of the brain were engorged and resembled a red veil stretched over the cerebrum. The cerebral convolutions were flattened, and there was a moderate increase in the amount of fluid in the subarachnoid space. Cross sections through the hemipshere revealed normal color and no gross hemorrhage or pigmentation such as is described in chronic malaria. Organs not mentioned were without significant change.

Microscopic Observations.—(*a*) Brain: The outstanding feature was the marked engorgement of the capillaries with ameboid forms of parasites and parasitized red cells. Many of the capillaries were occluded and formed bulblike dilatations. The cells making up the endothelial lining of the vessels bulged into the lumens, and many contained pigment. Some of the vessels contained fresh thrombi. There were areas of petechial hemorrhages and necrosis, in most of which the red cells were well preserved. The capillaries in the spinal cord also contained clumps of parasitized cells. There was no leukocytic reaction.

(*b*) Adrenal Gland: The cortex was well preserved. There were no areas of necrosis or vacuoles, no engorgement of the sinuses with red cells or parasites, yet the vessels in the fat beyond the capsule were literally distended with plugs of parasites.

(*c*) Kidney: There was an occasional scarred glomerulus. The capillaries were relatively free from parasites except in the medulla. Epithelial cells appeared swollen and had pale flaky cytoplasm. There was neither necrosis nor infarction.

(*d*) Liver: The hepatic cells showed evidence of cloudy swelling. The Kupffer cells stood out conspicuously, saturated with a yellowish brown pigment. The sinuses were narrow and contained occasional red cells, some of which were parasitized. There was no fatty degeneration.

(*e*) Stomach and Intestinal Tract: The capillaries of the mucosae of the stomach and the entire intestinal tract were engorged and contained parasitized red cells, but there were no hemorrhages and no ulcerations.

(*f*) Spleen: The spleen appeared identical with that in case 1.

(*g*) Bone Marrow: The marrow was not hyperplastic, nor was there any imbalance in the types of cells. There was no necrosis and certainly no reservoir of parasites; in fact, the sinuses of the marrow contained fewer parasites than

most of the tissues. This was contrary to a current notion that the parasites collect in the marrow.

(*h*) Lung: There was no infection; the capillaries contained parasitized red cells but did not appear as if they were occluded. The picture was that of edema. There was no evidence of pneumonia.

(*i*) Heart: The capillaries were so distended and plugged with parasites and thrombi that some of them literally bulged. The larger vessels were empty, but rows of parasitized red cells containing ameboid forms adhered to the intima. The endothelial cells lining the capillaries were swollen, and many of them contained pigment granules. There were patches of myocardial degeneration; the cell walls were still intact, but the cytoplasm was translucent and hydropic. Even in the center of some of these areas the cell walls had not disintegrated. There was no proliferation of fibroblasts and no leukocytic invasion, all of which would indicate an ischemic type of infarction. The blocks taken near the apex of the heart showed more plugging of capillaries than those from near the base of the heart. The musculature had a loose texture, indicating edema. There was no evidence of coronary sclerosis.

COMMENT

The extremely rapid course of the disease and the briefness of the hospitalization in both of these cases precluded early diagnosis with institution of treatment. In case 1, although the diagnosis of P. falciparum malaria was made on admission, the patient, a comparatively young man, had already collapsed, and treatment was of no avail. Because of the advanced age of the patient in case 2, the malarial nature of the cardiac lesions was not suspected until too late; the recorded blood pressure of 60 systolic and 40 diastolic, so usual in cardiac failure, served further to obscure the diagnosis. Death in both cases was typical of cardiac dilatation and collapse. Neither patient was in actual coma, but both of them seemed drowsy, even though they could be aroused.

One would experience considerable difficulty in distinguishing the types of malaria on the basis of the gross findings at autopsy except for the dilated heart with dark, reddish, soft musculature found in both of these cases, proved to be cases of P. falciparum malaria. It is not until the tissues are examined microscopically that the characteristic lesions of this type of malaria become unmistakable. My chief reason for selecting these cases is that the photomicrographs made illustrate these changes so closely.

Plugging of cerebral vessels has been demonstrated repeatedly and is always emphasized in discussions of the pathologic aspects of P. falciparum infection. One should not overlook the fact that the coronary system is as terminal in character as is the circulation of the brain and has as poor a collateral supply. Therefore, one should expect to find parasitic plugging or even thrombi in the coronary vessels as well as in those of the brain. It is only natural that the occlusion should begin in the most distal branches, the caliber of which is small, since the

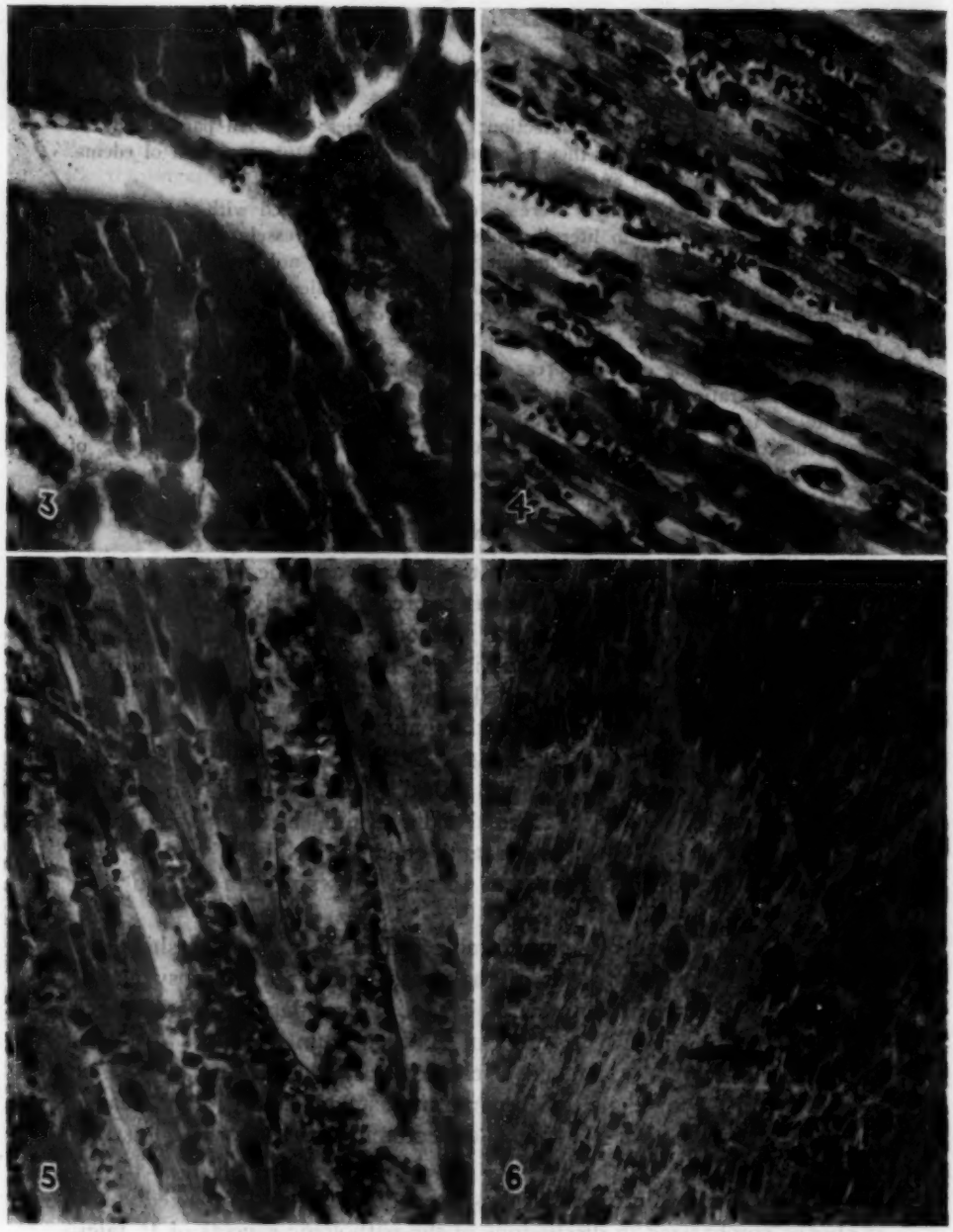

Fig. 3 (case 1).—Heart muscle showing a branching vessel occluded with parasites. In the large branch the parasites cling to the wall. The red cells free in the lumen contain relatively few parasites.

Fig. 4 (case 2).—Myocardium in acute P. falciparum malaria. All the capillaries are occluded with parasites. The endothelial cells lining capillaries are swollen, the muscle fibers have lost their striations, and early hydropic degeneration is present.

Fig. 5 (case 2).—Myocardium showing distended capillaries plugged with parasites. In the larger vessels rows of parasites adhere to the walls.

Fig. 6 (case 2).—Myocardium with a large area of degeneration. Note the absence of fibrosis. Many muscle fibers in the degenerated area still retain intact cell walls. Capillaries plugged with parasites are seen along the perimeter of degeneration.

process is not unlike embolism, even to having the same patchy distribution. The interval between occlusion and death may be so short that no discoloration occurs and grossly the heart wall shows no indication of the area involved, a situation which makes the selection of blocks difficult. I have found that the blocks taken from areas equidistant from the two coronary arteries and near the apex are most apt to show the lesions. Blocks should be from 1 to 2 cm. in thickness; otherwise the fixing fluid will wash out the engorgement and may even release the fresh plugs. These blocks should be fixed for periods of from twelve to twenty-four hours and then may be cut down to the proper size for complete fixation.

The striking tendency of the parasites and parasitized red cells to adhere to the capillary walls is clearly seen in the illustrations, and only the ameboid forms are lined along the inner surface of the vessels (fig. 3). The endothelial cells of the capillaries are swollen and often contain phagocytosed malarial pigment. I have not been able to demonstrate a similar phenomenon for Plasmodium vivax infections.

The lesions in the heart resemble infarcts in that they are rather sharply demarcated. Throughout them it is interesting to find the capillaries plugged with parasitized red cells, but there is neither hemorrhage nor leukocytic reaction, and the cell walls of the muscle fibers are intact. The areas are conspicuous because they stain poorly with hematoxylin and eosin and show no fat globules with fat stains; furthermore, all striations of the included muscle fibers are obliterated, and the cytoplasm is hydropic and flaky. These areas may be recent, and it is possible that after the segmentation of the parasites the circulation is resumed in the channels where the occlusions have not developed into thrombi, and the muscle fibers are restored to normal.

During the time that these occlusions exist, the organ must experience anoxemia proportional to the extent of the area involved. Clinically, therefore, the condition is like any other form of coronary occlusion, and the fatality in malaria due to P. falciparum will depend on the degree of occlusion and any added strain of the heart during the course of treatment.

I have included illustrations which show cerebral lesions and plugging of vessels. The marrow showed no change and no parasites, which contradicts the old theory that the marrow acts as a reservoir for the parasites. In the liver and the adrenal gland, the sinusoids were not clogged with parasites, and there was no tendency for the parasitized cells to cling to the vessel walls. The spleen appeared the same as in P. vivax infections.

Microscopic evidence indicates that the coronary occlusions producing anoxemia of the heart may be as important a factor in fatal cases of P. falciparum malaria as the occlusions of cerebral vessels.

SUMMARY

Ameboid forms of Plasmodium falciparum have a tendency to adhere to all capillary walls; consequently they may bring about occlusion, plugging or thrombosis. The progress of events indicates that this parasite may produce symptoms because of these mechanical factors. The coronary system of the heart offers a poor collateral circulation; hence plugging of coronary vessels is apt to create anoxemia of the myocardium, resulting in dilatation and collapse.

RETICULUM

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RETICULUM was first observed by Kupffer [1] in the liver and was described by him as a fibrillar network ramifying throughout the organ on the sinusoidal surfaces of the hepatic cords in close association with the stellate cells which bear the discoverer's name. Mall [2] distinguished reticular from collagenous and elastic fibers. He observed that the former were comparatively resistant to acid and alkaline solvents and digestive ferments and that they were made relatively distinct by such digestive preparation. Russakoff,[3] Kon,[4] Rössle and Yoshida [5] and others described reticulum in various organs throughout the body, including the liver, the kidney, the pancreas, the lymph nodes and the lungs. Reticulum as a product of granulomatous inflammatory processes, particularly in the presence of tuberculous infection, was described by Miller [6] and by Foot.[7] Studies of the histogenesis of reticulum were reported by Corner,[8] Foot,[9] Mallory and Parker,[10] Rinehart [11] and others, and the reticulum occurring in tumors was discussed by various contributors, notably White,[12] Niosi,[13] Foot and Day [14] and Mallory and Parker.[10] Their observations, as well as the various contributions to technical methods, will be referred to later.

During the past five years, my associates and I have prepared histologic sections of pathologic tissue for the demonstration of reticulum

From the Department of Pathology, Indianapolis City Hospital.

1. Kupffer, C.: Arch. f. mikr. Anat. **12**:351, 1876.
2. Mall, F. P.: Abhandl. d. math.-phys. Cl. d. k. sächs. Gesellsch. d. Wissensch. **17**:299, 1891; Johns Hopkins Hosp. Rep. **1**:171, 1896.
3. Russakoff, A.: Beitr. z. path. Anat. u. z. allg. Path. **45**:476, 1909.
4. Kon, Y.: Arch. f. Entwcklngsmechn. d. Organ. **25**:492, 1908.
5. Rössle, R., and Yoshida, T.: Beitr. z. path. Anat. u. z. allg. Path. **45**:110, 1909.
6. Miller, W. S.: Am. Rev. Tuberc. **7**:141, 1923.
7. Foot, N. C.: Am. J. Path. **1**:341, 1925.
8. Corner, W. G.: Contrib. Embryol. **9**:85, 1920.
9. Foot, N. C.: Am. J. Path. **3**:401, 1927.
10. Mallory, F. B., and Parker, F., Jr.: Am. J. Path. **3**:515, 1927.
11. Rinehart, J. F.: Am. J. Path. **6**:525, 1930.
12. White, W. C.: Bull. Johns Hopkins Hosp. **11**:209, 1900.
13. Speciale, F.: Tumori **10**:37, 1923-1924.
14. Foot, N. C., and Day, H. A.: Am. J. Path. **1**:681, 1925.

almost as a routine. It is the purpose of this report to summarize the experience thus accumulated, together with that previously made available by the aforementioned workers, regarding technical methods, the nature and the histogenesis of reticulum, its appearance in pathologic lesions, and particularly the practical importance of reticulum, such as it may be, in pathologic diagnosis.

TECHNICAL METHODS FOR THE DEMONSTRATION OF RETICULUM

The study of reticulum was stimulated greatly by the discovery of Maresch [15] that the ammoniacal silver nitrate solution originally devised by Bielschowsky [16] for impregnation of neurofibrils would demonstrate reticular fibers. Improvements were made chiefly by Perdrau,[17] who introduced the preliminary procedure of treating sections with potassium permanganate, Laidlaw,[18] who suggested that oxalic acid be used to secure additional reduction, following the usual toning with gold chloride, and Foot,[19] who provided more complete differentiation through addition of Van Gieson's trinitrophenol and acid fuchsin. Various modifications have been offered, and we have used all of them more or less. The method which we have found most serviceable is based on the principles laid down by the aforementioned contributors, with some modification of Masson's methods [20] being used when counterstaining is desired; it is essentially as follows, subject to modification according to individual taste and the variability of action of different samples of chemical reagents.

1. Fix tissue overnight or longer in solution of formaldehyde U. S. P. (1:10), dehydrate with any standard reagent and embed in paraffin. Cut sections at 6 to 8 microns. With abundant thick egg albumin containing a minimum of glycerin, fix sections to slides carefully kept free of paraffin and grease. In spreading the albumin, a finger should be used which does not come in contact with paraffin on handling blocks, and the albuminized slide should not come in contact with water until the section is ready to mount. Dry sections in an oven at 37 C. at least overnight, and for two days if time is allowed.
2. Deparaffinize and carry sections to water in the usual manner.
3. Place sections for five minutes in 0.25 per cent potassium permanganate.
4. Rinse in water.
5. Place in 2 per cent oxalic acid until colorless.
6. Wash in water, preferably running, for five minutes.

15. Maresch, R.: Centralbl. f. allg. Path. u. path. Anat. **16**:641, 1905.
16. Bielschowsky, M.: Arch. f. Psychiat. **39**:1321, 1905.
17. Perdrau, J. R.: J. Path. & Bact. **24**:117, 1921.
18. Laidlaw, G. F.: Am. J. Path. **5**:239, 1929.
19. Foot, N. C.: J. Lab. & Clin. Med. **9**:777, 1924.
20. Masson, P.: J. Techn. Methods **12**:75, 1929.

7. Place for two minutes in each of two changes of distilled water.

8. Place for forty-five minutes in 10 per cent silver nitrate.

9. Rinse thoroughly in two changes of distilled water; for example, wave the slide back and forth ten times in the first jar and thirty times in the second.

10. Place for thirty minutes in ammoniacal silver nitrate solution, made up as follows: Take 15 cc. of 10 per cent silver nitrate from the bottle used for step 8. (This will use up the solution at a rate sufficiently rapid to insure adequate freshness of silver nitrate solutions.) To this, add ammonia, one-third strength, dropwise but rapidly until the precipitate is nearly dissolved. The reaction is relatively slow, and the effect must be observed for at least thirty seconds before it is accepted as final. For the sake of economy of time, however, one may be bold in adding ammonia, as a small amount of silver nitrate can be added again if all the precipitate is dissolved. All that matters is that a few black grains remain on the filter paper. Filter the solution into the staining jar and, if necessary, add distilled water to bring the fluid level high enough to cover the sections. Mounting the section toward one end of the slide will promote economy.

11. Rinse as in step 9.

12. Place for five minutes in neutral solution of formaldehyde U. S. P. (1:10).

13. Wash thoroughly.

14. Place in 0.3 per cent gold chloride for three minutes or until sections turn gray.

15. Rinse in distilled water.

16. Place in 2 per cent oxalic acid for five minutes or until sections turn purple.

17. Rinse in distilled water.

18. Place for three minutes in 5 per cent sodium thiosulfate ("hypo").

19. Wash, preferably in running water, for five minutes.

If no counterstaining is desired, sections may be dehydrated and mounted by any standard method. If counterstaining is desired, the following additional steps may be carried out:

20. Place for five minutes in a mixture of equal parts of 1 per cent phloxine and 1 per cent ponceau 2R (called xylidine ponceau in the Masson technic) containing 0.1 per cent acetic acid.

21. Rinse briefly in 0.1 per cent acetic acid.

22. Place for fifteen seconds to five minutes in a solution containing 2 per cent orange G and 5 per cent phosphotungstic acid.

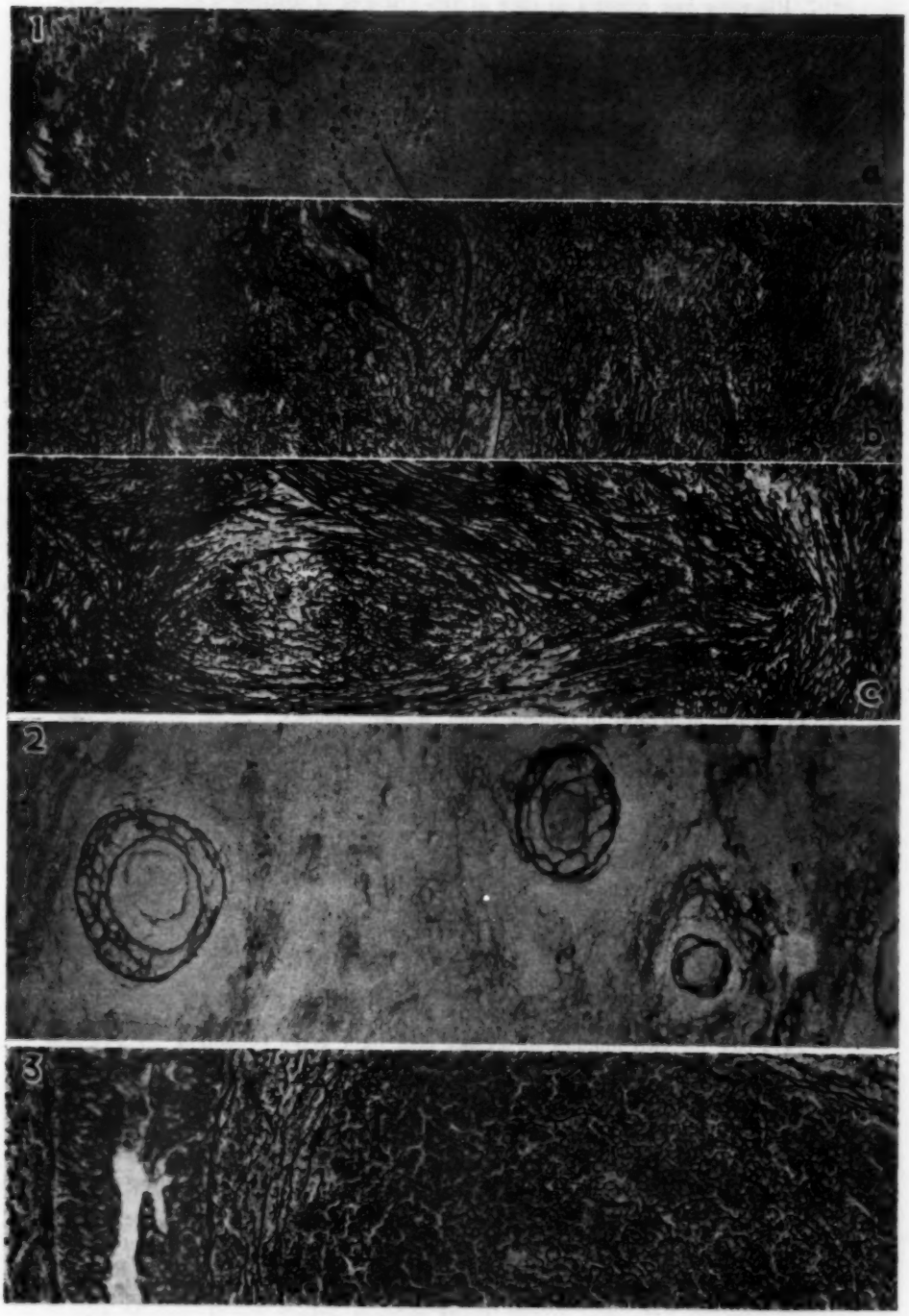
23. Rinse briefly in 0.1 per cent acetic acid.

24. Place for two minutes in 0.1 per cent light green containing 0.1 per cent acetic acid.

25. Rinse briefly in 0.1 per cent acetic acid.

26. Rinse briefly in 95 per cent alcohol (until the green ceases to run rapidly). Dehydrate for eight minutes in acetone, clear in xylene for ten minutes and mount in balsam or gum dammar. Results: reticulum black, nuclei gray, collagen green, cytoplasmic structures various shades of red to orange or brown.

Comment.—(*a*) Fixation: Repeated trial has proved to our satisfaction that solution of formaldehyde U. S. P. is the fixative of choice for reticulum. Reagents containing mercury, chromium or other heavy metals, while rendering very sharp the detail of collagen fibrils after the use of aniline blue, seem to us to produce



(See legend on opposite page)

relatively unprecise definition of silver-staining fibers, whether reticular or axonal; solution of formaldehyde U. S. P. yields adequate fixation of the most delicate fibrils. It will accordingly be found that the preparation of sections to show reticulum can be carried out with particular convenience in laboratories employing solution of formaldehyde U. S. P. as the routine fixative.

(*b*) Nature of the Silver Nitrate Solution and Its Relation to Loss of Sections from Slides: After considerable trial of different forms of ammoniacal silver nitrate solution, such as those prepared with lithium carbonate, sodium carbonate and sodium hydroxide, we are convinced that while the carbonate solutions may render a slightly heavier or more detailed impregnation, the difference between the results from carbonated and those from purely ammoniacal solutions is so slight as to be detected with difficulty in unlabeled serial sections prepared with the two methods. That this difference is of value in research may be questioned, and it certainly may be disregarded in routine pathologic practice. The alkali tends, in spite of tedious repeated washing of the precipitated silver carbonate or hydroxide in an attempt to wash out excess alkali, to digest the albumin and detach the sections from the slides. If, on the other hand, the slides are kept free of paraffin and grease by the precaution mentioned previously, if thick albumin is used generously and is not washed off prematurely, if the sections are dried overnight or, if possible, for two days, and if ammonium silver nitrate is used in the concentration given, failure of impregnation and loss of sections will occur rarely.

(*c*) Mordanting: I have failed to find anything better than the Mallory "bleach," applied by Perdrau to reticulum. Immersion in 10 per cent silver nitrate for forty-five minutes will be found adequate for intermediate mordanting or sensitizing. The use of ferric alum, recommended by Gomori,[21] and other reagents results, in our hands, in little improvement and frequently renders a picture in which the tissue as a whole, including reticulum, lacks the richness of texture produced by Perdrau's method.

(*d*) Counterstain: It will be found that the Perdrau technic, followed by reduction of gold with oxalic acid as suggested by Laidlaw, yields a picture requiring little counterstain and serving most routine laboratory needs. Collagen fibrils are rose colored or brown and are fairly easily distinguished from reticulum. In routine practice one wishes to know, not how much reticulum there is in proportion

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EXPLANATION OF FIGURES 1, 2 AND 3

Fig. 1.—Tuberculosis of a hilar lymph node: (*a*) Border of a necrotic area; hematoxylin and eosin; × 125. (*b*) The same field; Perdrau's method; × 133. There is a slight rotation of the section on the slide compared with *a*. (*c*) Another field in the same section; Wilder's method; × 278. This shows the characteristic tuberculoid pattern of reticulum at the site of a tubercle. When prepared with hematoxylin and eosin, this whole field was completely lacking in detail.

Fig. 2.—Section from a gumma of the brain; Perdrau's method; × 267. It shows the characteristic lamellar reduplication of reticulum about the narrowed lumens of blood vessels. All tissue of this section was largely lacking in detail when prepared with hematoxylin and eosin.

Fig. 3.—Adenoid tissue; Laidlaw's method; × 178. It shows absence of reticulum in the modified squamous epithelial lining of a crypt. Part of a follicle is seen; in it the reticulum is relatively sparse.

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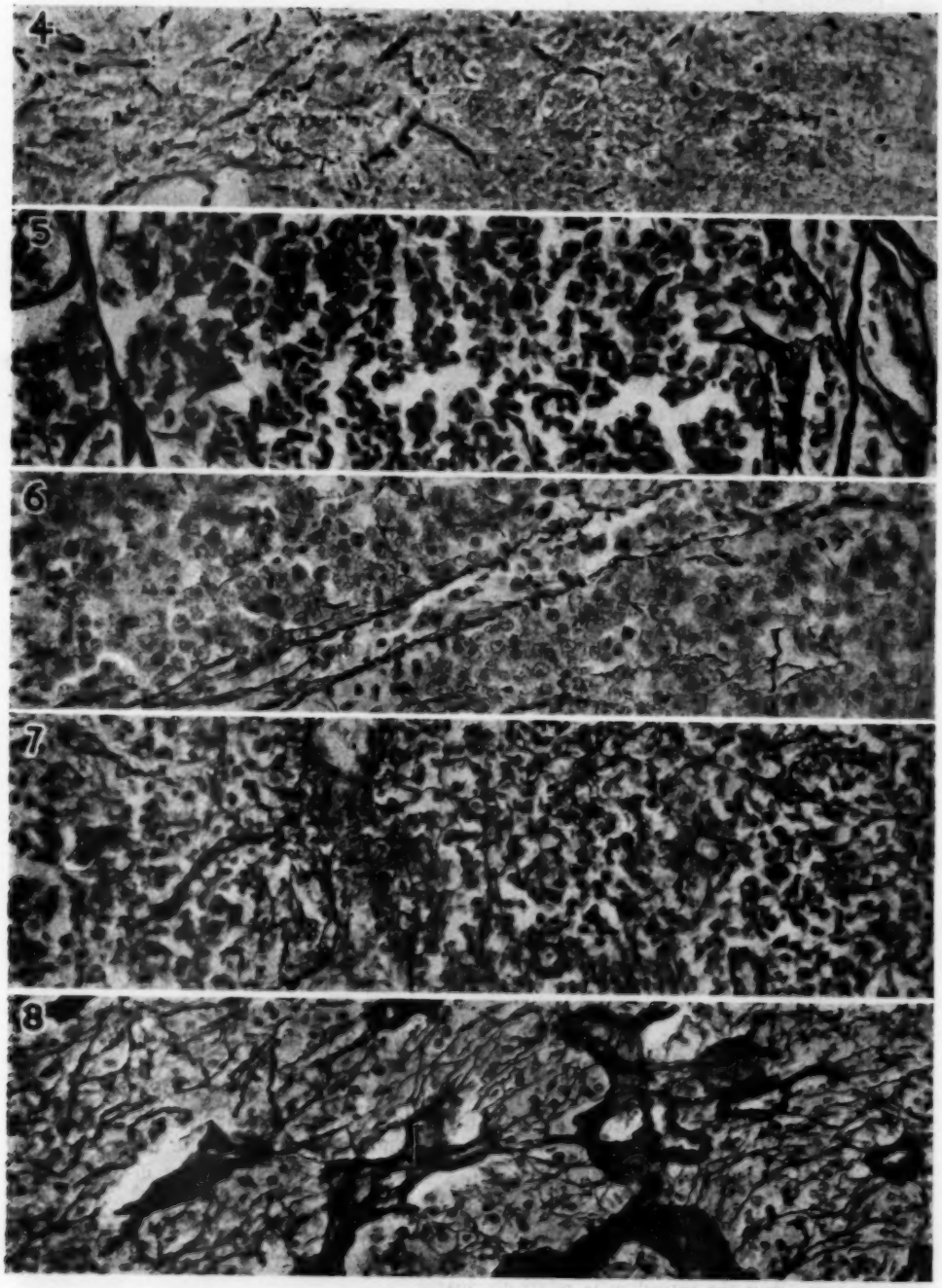
21. Gomori, G.: Am. J. Path. **15**:493, 1939.



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to collagen, but simply what the total reticular pattern is; i. e., is there or is there not reticulum between the tumor cells? Inasmuch as collagen has essentially the same diagnostic significance, confusion of collagen with reticulum will not matter greatly. One cannot expect, however, to show collagen as such brilliantly with an uncounterstained section prepared for reticulum. It will be found that the more delicate the counterstain the clearer the reticular pattern is. It is, for example, very easy to override the section too darkly with aniline blue. For this reason, a stain for Nissl substance is useful, as the thionine or the cresyl violet will enhance the nuclear pattern but will leave the network relatively bare. (Take sections previously stained for reticulum and immerse in 1 per cent aqueous thionine or cresyl violet for five minutes; rinse in water, rinse quickly in 95 per cent alcohol, dehydrate five minutes in absolute alcohol, clear in xylene and mount in balsam or its equivalent.) Masson's light green is an admirable collagen stain because it is reasonably intense and specific but treats fibrils with comparative delicacy and does not "steal from" reticulum as aniline blue frequently does. The use of the red and orange ingredients is more or less effective in completing the tissue detail. It will often be found that cytoplasmic and intercellular structures, collagen perhaps excepted, do not stain so well after the reticulum method has been used as after staining with hematoxylin. This is not so much the case after the use of methods for axis-cylinders, in which event, for example, healthy myelin can be stained orange quite faithfully. It is, in fact, advantageous to stain serial sections for reticulum and for nerve fibers; all one has to do is to prepare one of the sections by passing it through steps 4 to 7 while the other stays in water, and then carry both together through the remainder. This will yield the highly effective results of combined staining of nerve tissue [22] and rather complete staining of reticulum. To obtain certain varied results, a third section can be prepared by Bodian's method [23] as far as reduction of the protein silver with hydroquinone. The section may then be placed in water (step 13) and carried the rest of the way with the other slides.

(*e*) Cumbersomeness of the Method: Preparation of sections for the demonstration of reticulum in the busy laboratory may well be viewed with skepticism because

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EXPLANATION OF FIGURES 4 TO 8

Fig. 4.—Lymphosarcomatous infiltration of skin; Perdrau's method; × 273. Scarcely any reticulum is seen except about vessels and in the main connective tissue bundles.

Fig. 5.—Lymphosarcoma of a lymph node; Perdrau's method and thionine, × 318. There are foci relatively free of reticulum. Thick bands are stained, as well as fibrils.

Fig. 6.—Lymph node; Perdrau's and Masson's methods; × 273. A diagnosis of reticulum cell sarcoma was made by three experienced pathologists, our own opinion not being represented in the diagnosis. Reticulum is relatively sparse.

Fig. 7.—Brain showing perivascular sarcomatous proliferation of reticuloendothelial type; Laidlaw's method and thionine, × 227.

Fig. 8.—Hemangioblastoma of meninges; Laidlaw's method and thionine; × 227.

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22. Dublin, W. B.: J. Neuropath. & Exper. Neurol. **2**:205, 1943; Arch. Dermat. & Syph. **50**:361, 1944.

23. Maximow, A. A., and Bloom, W.: A Text-Book of Histology, Philadelphia, W. B. Saunders Company, 1930, pp. 95-96.

of the time and the labor required for its performance. It will be found, however, that by devoting a corner of a cupboard to a permanent row of staining jars containing the appropriate solutions, together with accessories, such as a small flask for preparing the ammoniacal silver nitrate solution and a dropping bottle for ammonia, labor is reduced to a minimum. The silver nitrate (if any of this is left in the staining jar, keep the cupboard closed to exclude light), the solution of formaldehyde U. S. P., the gold, the oxalic acid and the sodium thiosulfate may be used for a surprisingly long time. The jars for rinsing in distilled water, if kept

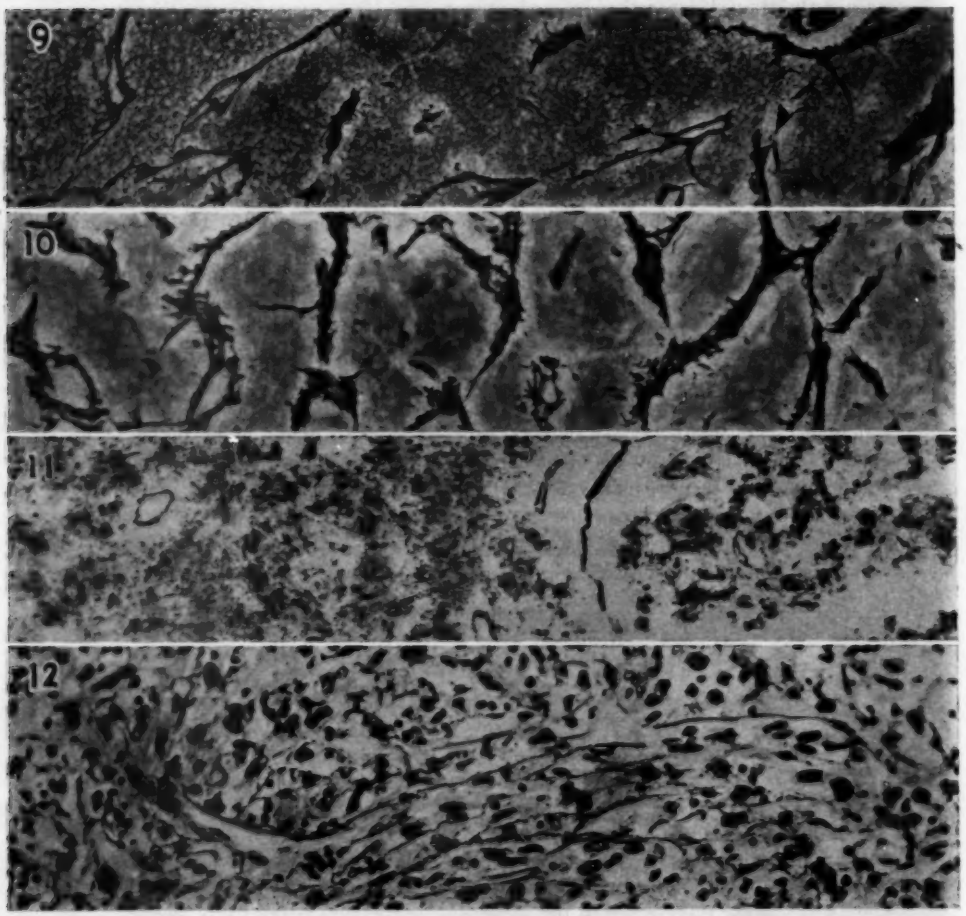

Fig. 9.—Neuroblastoma showing no intercellular reticulum; Laidlaw's method; × 130.

Fig. 10.—Ewing's tumor showing no intercellular reticulum; Perdrau's method; × 174.

Fig. 11.—Granulosa cell tumor showing absence of reticulum except for stroma and blood vessels; Perdrau's and Masson's methods; × 130.

Fig. 12.—Hypernephroma, in which both the histologic pattern and the reticulum simulate sarcoma; Perdrau's and Masson's methods; × 261.

permanently in place, need only be emptied. (Caution: The jar used for first rinsing after sections have been removed from the ammoniacal silver nitrate solution, the flask used for making up the ammoniacal silver nitrate solution and the jar used for staining with that solution should be rinsed out carefully to avoid the gradual production of silver fulminate, with the danger of explosion later on.) If to the foregoing one adds the custom of running ammonia in rapidly, adding a small excess of silver nitrate if need be, one has a staining routine for reticulum and for nerve tissue which is facile and reliable enough to meet the demands of any laboratory, however busy, which has a place for the use of essential special methods in histologic diagnosis.

NATURE OF RETICULUM

It seems to be pretty well agreed that connective tissue fibers may be recognized in three forms: collagen, reticulum and elastin. Reticulum and collagen have properties which differ in some respects, although having in the main a close affinity. There is some difference of opinion on this last-mentioned subject (relation of reticulum to collagen), the views being that: (1) reticulum and collagen are one and the same,[10] (2) reticulum and collagen have the same chemical properties but have slight differences of physical state and (3) reticulum and collagen differ physically and chemically. Maximow and Bloom [23] stated that although collagenous fibers, in the general opinion, do not branch, reticular fibers do. The first fibers to appear when collagenous tissue is formed in the embryo or in the adult body are argyrophil networks; these are gradually transformed into collagenous bundles. The methods generally used for the demonstration of collagenous fibers do not stain reticulum distinctly. Mall [2] showed by digestion experiments that reticulum is comparatively resistant to acid and alkaline solvents and digestive ferments. Foot [7] made particular use of his differential staining method in demonstrating that reticulum appears to be a precursor of collagen and that its fibers are gradually collagenized, in other words, that reticulum is precollagen. A study especially of tuberculous lesions leaves one with an impression that this relation of reticulum to collagen is amply supported. The argentophilic fibers can be seen to pass almost imperceptibly into the developing collagenous tissue. Depending on whether acid fuchsin, light green or aniline blue is used, varying amounts of tissue give the staining reaction for collagen and for reticulum. It is of note that acid fuchsin, used to stain collagen in the Van Gieson method, may be used in the modified Masson method, yet will yield to the stronger effect of light green or aniline blue.

Further than the foregoing statements there is little of a definite or proved nature that can be said of the chemical or the physical properties of reticulum. Mallory and Parker [10] reached the conclusion that reticulum and collagen are identical as a result of their observation that

when certain connective tissue fibers are found singly they give the staining reaction for reticulum but when they join a bundle of fibers they appear as collagen. That this view is open to question can be shown easily by use of a combined staining method. Separate fibers will, in a section stained in this way, commonly appear blue (or green) or black, and different portions of the same fiber may appear irregularly blue or black. It will further be found that thick fibers or bundles of fibers, apparently homogeneous when prepared routinely, frequently show a heterogeneous mixture of blue and black fibers when stained for reticulum and collagen. This is particularly true of the collagenous, argentophilic bands seen in the central or fibrous portions of rheumatic nodules. Broad bands of fibrous tissue when stained specially will frequently stain entirely black. We therefore take the view that reticulum is a precursor of collagen and is quite similar to, but chemically and physically different from, collagen.

HISTOGENESIS OF RETICULUM

Differences of opinion concerning the method of the formation of reticulum are bound up to some extent with factors referred to in the preceding paragraph. Mallory and Parker,[10] for example, expressed the belief that reticulum is produced only by fibroblasts, but this belief is confronted with the same difficulties which face the concept of identity of collagen and reticulum. That reticulum and collagen are produced by fibroblasts cannot be denied, for pure fibroma possesses abundant reticulum. So also, however, do pure collections of epithelioid cells or of lymphocytes, and it seems necessary, therefore, to accept the view that reticulum originates from all the aforementioned types of cells. It is well to bear in mind also that reticular cells, precursors of fibroblasts, are commonly found in association with collections of fibroblasts. This can be shown with Hortega's methods as well as with certain routine ones.

There seems to be little question that reticulum can be laid down by perithelial reticuloendothelial cells and that it ramifies freely in the various layers of the vessel wall, outlining the intima clearly. Whether reticulum is formed by vascular endothelium (excluding that of lymph node sinuses) and/or connects directly with endothelial cells is not agreed on. Corner [8] and Rinehart [11] demonstrated to their satisfaction that reticular fibers arise in, extend from and are in direct connection with vascular endothelial cells. Foot,[24] on the other hand, was unable to demonstrate that reticular fibers connect directly with cell bodies in the way that dendrites join the cell bodies of neurons. Foot con-

24. Foot, N. C.: Am. J. Path. 3:401, 1927.

sidered reticulum to be the precipitated form of an intercellular substance secreted by reticuloendothelial cells and viewed collagen as a chemical substance in tissue juices that impregnates fibers, rather than as the sole constituent of white fibrous tissue.

I have made no special study of the problem of the histogenesis of reticulum but have gained the impression that it originates from multiple cell types, as explained previously. I have also received the impression that reticular cells and reticulum have no definite connection, the cells lying along the fibers and on occasion rounding up and detaching themselves from the reticular framework.

PATHOLOGIC OBSERVATIONS ON THE RETICULUM OCCURRING IN THE SEVERAL TYPES OF GRANULOMA

Tuberculosis.—In a tubercle the deposition of reticulum accompanies the proliferation and differentiation of reticuloendothelial cells; these become epithelioid cells. The fibers course in a rich network among these cells and also are seen among the peripherally situated lymphocytes. If complete caseation or liquefaction occurs, all details of the tissue are obliterated; reticulum is affected with the rest of the tissue and merits no special mention in this regard. It will, however, be observed frequently that tissue foci, varying greatly in color from yellow to white and in consistency from firm and fibrous to edematous or gelatinous, when sectioned and stained with hematoxylin and eosin will appear homogeneously pink and will show no detail, thus meriting a classification at least of coagulative necrosis; this completely characterless tissue nevertheless shows many reticular fibers when stained appropriately. The significance of this fact will be discussed after the findings in syphilis have been described.

Syphilis.—Reticulum is found in abundance in the gumma. It is present among proliferating plasma cells, lymphocytes and histiocytes, where no reticulum previously existed and where no fibroblast can be identified, and is seen in the walls of blood vessels. When the latter show a characteristic reduplication of the intima in layers, sections appropriately prepared show multiple concentric bands of reticulum. Since the necrosis in the gumma results from obliterative endarteritis with attendant ischemia, the tissue pattern remains to some extent, and reticulum is easily identified. It should be emphasized, however, that foci will be found in which all detail is lost.

Most authors comparing reticulum in tuberculosis with that in syphilis state that reticulum can be found in the gumma but rarely in the tubercle. Our finding is that although in the main the tendency for caseation to wipe out tissue structure is greater in tuberculosis, it is

unsafe to rely on the presence or the absence of reticulum as a crucial diagnostic factor. The pattern of the reticulum which is brought out in an apparently characterless tissue is of much greater significance than the amount. In the gumma the aforementioned concentric lamellas indicate the endothelial proliferation occurring in the original lesion. None of this is seen in the tubercle; in this structure, if anything different from the original tissue pattern is seen, it is of a type which would result from formation of fibers between semiradially disposed epithelioid cells. The difference thus is qualitative rather than quantitative.

Blastomycosis.—Miller [25] reported a case of pulmonary blastomycosis in which the reticular pattern did not differ from that in tuberculosis. In the single specimen available to us for study, a cerebral lesion, the granuloma contained a purulent element which dissipated the tubercular pattern and made it much less regular than that ordinarily seen in tuberculosis. In foci of polymorphonuclear infiltration reticulum is relatively scant. This results in a pattern of reticulum which is less regular than that in tuberculosis and in which blank pockets are found corresponding to microscopic abscesses. No specific feature is observed in the reticular pattern which is characteristic or of diagnostic significance.

Coccidioidosis.—The findings are essentially those of blastomycosis.

Actinomycosis.—The findings are the same as in the coccidioidal and the blastomycotic granuloma. In these three conditions, diagnosis must rest on finding the specific organisms. Incidentally, methods that demonstrate reticulum leave yeast and fungi strongly impregnated, and silver preparations in general, including strong protein silver, show Actinomyces as black filaments. Yeasts and fungi, however, can be shown as red bodies with carmine, according to the method of Kernohan,[26] even though strong protein silver is used to stain the background.

Rheumatism.—The reticular fibers in Aschoff bodies are found arranged irregularly in relation to the specific inflammatory cells. In the central fibrous cores of the rheumatic nodules the reticulum is seen intermingled with fibers which take the stain for collagen. Some broad fibrous masses give homogeneously the reaction for reticulum. Although this is an interesting observation, it is not of crucial diagnostic importance. The diagnosis of a rheumatic nodule must be made on the basis of features revealed by sections prepared routinely.

Gout.—In gout, round, ovoid or clover leaf foci are surrounded by encapsulating strands of reticulum and collagen in which atypical, characteristic aggregations of foreign body giant cells are found. Cleft for-

25. Miller, W. S.: Am. J. Path. **3**:315, 1927.

26. Kernohan, J. W.: J. Neuropath. & Exper. Neurol. **2**:95, 1943.

mation is prominent. In the central masses, homogeneous in routine sections except for clefts, very fine reticular fibers, almost disappearing into an amorphous state, are seen in sparse bundles which have an interweaving tendency and are related to the bundles of uric acid crystals and which, if they extend to the capsular bundles, merge with the latter. This picture is rather characteristic. It does not, however, add anything of great diagnostic value to the picture seen in sections stained with hematoxylin and eosin or those prepared with methods designed to show gout specifically.

Sarcoid of Boeck.—Reticulum is laid down by the epithelioid cells in a form similar to that noted in straightforward tuberculosis. Giant cells are seen infrequently and caseation scarcely at all, but there is no difference between the reticular patterns. This feature, therefore, shows a histologic affinity of the two conditions but is of no particular help in their diagnosis.

Leprosy.—The histiocytes of leprosy deposit reticulum freely. The pattern varies according to that of the histiocytes, as tuberculoid or lepromatous, and adds no information otherwise.

Idiopathic Reticuloendothelioses.—In Gaucher's disease, in the Niemann-Pick syndrome and in similar conditions, reticulum is deposited freely among the histiocytes. The amount varies; probably the more rapidly the reticular cells proliferate the less abundant is the reticulum. This appears to be true in a broad sense of inflammatory proliferations in general; for example, in lymphocytic infiltrations, when the cells pour forth rapidly, little or no reticulum may be found, whereas in a lymphocytic aggregation which gathers slowly and with some degree of organization, perhaps even simulating a follicle, reticulum may be abundant and even collagen may appear in varying quantities.

Comment.—In the specimens of granuloma available, certain specific characteristics are seen. While these are illuminating and are recorded for completeness, they are rarely of diagnostic value. As in the past, reticulum preparations are of value in distinguishing a gumma from a tubercle in certain cases. It is suggested that the presence or the absence of reticulum in such lesions be not depended on too strongly and that emphasis be placed on the obliterative endarteritic pattern of the gumma or the tuberculoid pattern in tuberculosis, wherever either of these can be demonstrated.

PATHOLOGIC OBSERVATIONS ON THE RETICULUM OCCURRING IN NEOPLASMS

Tumors of Fibroblasts.—Foot and Day [14] stated that fibroma contains abundant collagen but no reticulum. Mallory and Parker [10] were

of the opinion that tumors of fibroblasts contain reticulum but that the latter is only a form of collagen. We find that fibroma and fibrosarcoma contain abundant reticulum, and frequently collagen, with moderate variation. Collagen is less abundant in the cellular, anaplastic forms, but reticulum appears to be abundant in all forms, with no dependable relation to the degree of differentiation. Myxoma, myxosarcoma, or tumors of fibroblasts containing myxomatous elements have a property of forming reticulum similar to that of fibroma or fibrosarcoma. Neurofibroma, so-called, and fibroblastic tumors of the meninges will be mentioned later.

Tumors of Muscle, Noncancerous and Cancerous.—Myoma and myosarcoma were said by Foot and Day [14] to contain reticulum and collagen in varying degrees of abundance, reticulum perhaps being converted into collagen. We have been able to confirm this finding. Again, the degree of differentiation does not invariably predict the abundance of formation of reticulum. We also share the opinion of the same authors that rhabdomyosarcoma forms abundant reticulum. No reference was found to reticulum occurring in granular cell myoblastoma. Stout [27] expressed the opinion that in neoplasms of this type the amount of reticulum varies greatly. In the single specimen of granular cell myoblastoma available to us for study (incidentally, one behaving as a cancer), reticulum was found only investing the organoid nodules; it did not pass between the individual cells. This failure of an accumulation of muscle cells to conform to what appears to be a general rule concerning muscle and fibrous tissue is comparable to what has emerged as a general phenomenon in the course of this study: the unaccountable variability with which reticulum is deposited by cells of the same type in the same tissue section.

Tumors of Fat Cells.—Reticulum is deposited abundantly between the individual cells of lipoma and liposarcoma. In other words, adipose tissue acts in the same way as fibrous and muscular tissue.

Tumors of Cartilage and Bone.—Neoplastic tissue containing histologically benign cartilage and bone contains little or no reticulum. We agree with Foot and Day,[14] however, that cellular areas in chondrosarcoma or osteosarcoma show abundant reticulum and collagen. In this regard the chondroblast, the osteoblast, the fibroblast and the myoblast exhibit a familial relation.

Foreign Body Giant Cell Tumors.—Foot and Day [14] found these neoplasms not to be rich in reticulum and to contain only moderate amounts of collagen. It is our experience that reticulum and collagen

27. Stout, A. P.: Personal communication to the author.

are present in abundance, although with variation, especially in xanthomatous or granulomatous areas. These tumors thus compare with other connective tissue neoplasms or granulomas.

Tumors of Blood and Lymph Vessels.—As one would expect, hemangioma and lymphangioma show abundant reticulum outlining the walls of the vascular spaces, and collagen is present in adventitial tissue and areas of hyaline fibrosis. Hemangioendothelioma and lymphangioendothelioma (the picture in Lindau's disease will be described later) have reticulum outlining the blood spaces. Fibers radiate from the vessel walls and traverse the cellular tissue in abundance but vary in number from field to field and vary from a few fibrils tentatively exploring the periphery of the cell masses to a dense network investing nearly every cell. This illustrates again the variability of reticulum. It also shows that reticulum is found in the cell masses of malignant endothelioma. Foot and Day [14] stated that reticulum is found closely investing the cells of malignant endothelioma of lymph nodes. Our impression is that while, as already stated, reticulum is present and varies in amount, the degree of abundance on the average is moderate, not quite equaling the degree observed in sarcoma. A noteworthy exception to this whole group is Ewing's endothelial myeloma, considered widely to be a type of hemangioendothelioma. Foot and Day [14] found less reticulum and more delicate fibers in this than in the ordinary type of hemangioendothelioma. We have examined tissue from well documented specimens of Ewing's tumor and have found practically no reticulum except for that lining the blood vessels and a rare abortive perithelial twig. With regard to reticulum formation, Ewing's tumor differs not only from endothelioma but also from mesenchymal tumors in general. The failure to show reticulum in the cellular tissue of tumors of this type (Ewing's) is disappointing because it renders this staining method valueless in distinguishing Ewing's tumor from neuroblastoma—often a difficult distinction in the best hands and one leading to wide difference of opinion among eminent pathologists having abundant experience with these two tumor types, when they have reviewed sections belonging to one or the other of the two disease groups.

Lymphosarcoma.—Foot and Day [14] observed reticulum in lymphosarcoma, malignant reticuloendothelioma and Hodgkin's disease, and collagen in the latter, abundantly and without great discrimination. Callender [28] stated that in lymphatic leukemia, giant follicular hyperplasia and lymphosarcoma the reticulum of lymph nodes is not increased but is distended or separated by tumor cells. Foot and Day [14] found new reticulum deposited among lymphocytes where the tumor penetrated the capsule. We have found considerable variation in

28. Callender, G. R.: Am. J. Path. **10**:443, 1934.

abundance of reticulum in lymphosarcoma and the nodes of patients with lymphatic leukemia but, on the whole, we have noted a generous amount, commonly investing individual cells. That new reticulum is formed is shown by its being deposited in extracapsular neoplastic tissue. One also should consider that if one were to reduce an average lymphomatous node to its original size, the reticular network would form a mat so dense that scarcely any room would be left for lymphocytes. We are in agreement with Foot and Day [14] that both reticulum and collagen are found in abundance in Hodgkin's disease, although the amount varies greatly. In sections of skin from a patient with mycosis fungoides, reticular and collagenous fibrils were present in abundance. The question of reticular cell sarcoma requires special attention. Callender [28] stated that in reticular cell sarcoma a delicate network of reticulum is found investing every tumor cell, and he laid emphasis on this as a diagnostic feature. Foot and Day [14] in reference to malignant reticuloendothelioma reported finding some reticulum but added that it often traversed many cells without branching. Warren and Picena [29] stated that a dense network of reticulum might be observed, or only scattered, fragmented fine threads, little reticulum often being seen within the cell masses. They therefore minimized the importance of reticulum in the diagnosis of reticular cell sarcoma. This problem is complicated by the lack of general agreement as to just what reticular cell sarcoma is. Warren and Picena [29] used the term in a restricted sense, describing the reticular cells as the primitive mesenchymal cells and stating that in neoplastic formations they are seen in syncytial masses, the protoplasm being undivided or slightly fenestrated, with oval or indented nuclei, well defined nuclear membranes, sparse powdery chromatin granules and one or two prominent nucleoli to a cell, giving the nucleus an "empty" appearance. An admixture of lymphocytes was noted commonly, pure tumor types being found but infrequently, and the predominant cell type being used for classification. Ewing [30] showed one illustration which is obviously from a case of giant follicular hyperplasia, and various other contributors have differed widely in criteria of classification. We have come to regard the main cell of the germ follicle as a young lymphocyte. Actually, all of this makes little difference. We share the opinion of many others that lymphoid tumors overlap in cell type so extensively that they should be grouped together, a subclass being appended to the diagnosis in the making of a report, and type differences being used only as broad guiding principles in attempts to predict radiosensitivity and clinical course. We

29. Warren, S., and Picena, J. P.: Am. J. Path. **17**:385, 1941.

30. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 425.

have observed further that reticulum is deposited in all forms of lymphosarcoma, including Hodgkin's disease, with wide variation and with no constant relation to cell type. In the reticular pattern of a histologic section of lymphosarcoma, nonfibrillar pockets may be found, with intervening foci of dense reticulum. Aside from natural variation, some of this may result from difference in rate of growth. In a certain case of lymphoblastoma cutis, in which one of numerous and repeated tumefactions appeared almost overnight, practically no reticulum could be shown. Reticulum is present indiscriminately in neoplastic and inflammatory nodes, and therefore is of no help in the diagnosis of borderline conditions. It is of interest that enlarging follicles of both adenitis and follicular lymphoma are relatively free of reticulum when compared with the surrounding lymphocytic tissue.

One must conclude, therefore, that reticulum is deposited indiscriminately by all members of the lymphoma family and is of little practical value in diagnosis; at least it adds nothing to the picture revealed by routine methods.

Adenoma and Carcinoma.—Epithelial neoplasms contain reticulum about the cell acini, but the acini themselves contain, if any, only rare, abortive peripheral reticular fibers. In this we are in accord with Foot and Day.[14] Reticular preparations may be used along broad lines in distinguishing epithelial from connective tissue or other mesenchymal neoplasms in difficult cases. It should be borne in mind, however, that occasionally carcinomatous acini can be quite small, and investment of these small acini may give a picture easily confused with that of sarcoma. This occurred in a pseudosarcomatous form of hypernephroma. In the group of epithelial neoplasms one may include seminoma, dysgerminoma and mixed tumors of the salivary glands (as regards epithelial acini). The relation between granulosa cell and theca cell tumor of the ovary deserves special comment. We have been able to confirm the finding of Wolfe and Neigus [31] that reticulum invests the individual theca cells but not the granulosa cells. Neoplasms of the anterior lobe of the pituitary gland behave as do adenoma and carcinoma of other glandular organs. No reticulum is found in the epithelial acini of lymphoepithelioma. We agree on this point with Cappell.[32] This tends to place lymphoepithelioma in the class of carcinoma, perhaps a modified squamous cell type.

Tumors of Nerve Origin.—We agree with Foot and Day [14] that glioma, ganglioneuroma, neuroblastoma and other tumors primarily of nerve origin contain no reticulum. Tumors of the meninges deserve special mention. We have been unable to recognize an endotheliomatous

31. Wolfe, S. A., and Neigus, I.: Am. J. Obst. & Gynec. **42**:218, 1941.
32. Cappell, D. F.: J. Path. & Bact. **33**:429, 1930.

form of meningioma in the sense commonly accepted. In 5 cases of true hemangioblastoma, in 1 of which the tumor was associated with Lindau's disease, reticulum was found outlining the blood vessels and extending into the cell acini in amount varying from scant to abundant. Usually the cell pattern shown by routine stains will reveal the angioblastic nature of these tumors. In 2 of our 5 cases, in both of which a diagnosis of astrocytoma had been made previously, it was possible to demonstrate both reticular and fine collagenous fibers radiating abundantly from the blood vessels among the tumor cells, and fat stains showed lipid droplets in the cytoplasm. Emphasis has been placed commonly on reticulum in hemangioblastoma in Lindau's disease, but study of most illustrations shows only the outline of the vascular spaces. This adds nothing to the hematoxylin-eosin or other routine preparation, which shows the characteristic picture of hypertrophied, often vacuolated endothelial cells forming acinous masses. Demonstration of reticular fibers among the individual cells, already mentioned, is entirely a different matter, and a positive result, if obtained, may be of great importance. It may be stated here that this principle is true of neoplasms in general. Reference is commonly found to the abundant reticulum found investing the acini of carcinoma and scattered in its stroma. It would be much more to the point to refer to the presence or the absence of reticulum among the individual tumor cells, and this should be the meaning in any unqualified reference to reticulum in a section of neoplastic tissue.

With regard to the more common varieties of meningioma (excluding hemangioma, which is like that elsewhere), namely, meningiotheliomatous, fibromatous (so-called dural endothelioma) and sarcomatous, we have found modest amounts of reticulum in the meningiotheliomatous type, occasional fibers penetrating the cell masses for varying distances, and abundant amounts in fibroma, fibrosarcoma and perithelial sarcoma, including perivascular lymphosarcomatous proliferations. In neuropathology this is the basis of a valuable and common use of methods of demonstrating reticulum. It can be stated with little reservation that every diffuse or cellular intracranial neoplasm not having some obvious specific feature requires preparation for the demonstration of reticulum and collagen along with the usual neurologic methods before one can say that it has been studied adequately. In this way, glioblastoma and sarcoma can be separated in many cases which otherwise might offer difficulty. Bailey,[33] and Globus[34] and practically every other discusser of intracranial sarcoma are agreed on this point.

33. Bailey, P.: Am. J. Clin. Path. **13**:478, 1943.

34. Globus, J. H.; Levin, S., and Sheps, J. G.: J. Neuropath. & Exper. Neurol. **3**:311, 1944.

Any tumor of a nerve sheath, which we regard as schwannoma in most cases, deposits reticulum abundantly and collagen irregularly. Cancerous schwannoma forms varying amounts of delicate reticular fibrils.

Nevi and Melanoma.—Benign and cancerous nevi contain some reticular fibers. Foot and Day [14] describe reticulum in melanosarcoma as penetrating the alveolar masses rather freely. Our own experience tends to place melanoma midway between sarcoma and carcinoma in content of reticulum. From this point of view, tumors of this type may be classed as modified epithelioma.

SUMMARY

Reticulum is a fibrillar substance closely related chemically and physically to collagen but differing from it on the basis of the staining by silver solutions, aniline blue, light green and other histologic reagents and of resistance to digestion by acids, alkali and gastric ferments. It is probably formed by intercellular precipitation of a secretion produced by reticular cells, histiocytes, monocytes, lymphocytes, vascular endothelium and fibroblasts, and also muscle, both smooth and striated. It is closely applied anatomically to the aforementioned cells but does not connect directly with the cell bodies. Reticulum is precollagen. Collagen is a chemical substance which impregnates fibers, probably reticular, thus forming what one knows as collagenous fibers.

Reticulum is demonstrated with ease and reliability sufficiently great to warrant use of appropriate methods in standard pathologic diagnosis. The method recommended embraces formaldehyde fixation, paraffin embedding, preparatory treatment of sections with potassium permanganate and oxalic acid, followed by immersion in silver nitrate solution, ammoniacal silver nitrate solution, solution of formaldehyde U. S. P., gold chloride solution, solution of oxalic acid and solution of sodium thiosulfate. Counterstaining, if used, consists of treatment with thionine or cresyl violet or with light green, ponceau and orange G.

Granuloma and lesions of the reticuloendothelial system produce reticulum in varying degrees of abundance, often in a characteristic pattern. The distinction of gumma from the tubercle of tuberculosis depends not so much on whether reticulum persists in necrotic tissue as on whether or not the lamellar endothelial reduplication in syphilis or the tuberculoid pattern in tuberculosis can be demonstrated; otherwise, the study yields nothing of diagnostic interest regarding the several types of granuloma. Methods that demonstrate reticulum render yeasts and fungi black.

Certain neoplasms are often distinguished with the help of methods for the demonstration of reticulum. Leiomyosarcoma, rhabdomyosar-

coma, fibrosarcoma, liposarcoma, the cellular portions of chondrosarcoma and osteosarcoma and other similar cancerous tumors of connective tissue origin, schwannian sarcoma and the theca cell tumor contain intercellular reticulum in varying degrees of abundance. Glioma, neuroblastoma, other tumors of purely neurogenic origin, adenoma, carcinoma, including seminoma, dysgerminoma, granulosa cell tumor, lymphoepithelioma, tumors of the anterior lobe of the pituitary gland, the epithelial portions of mixed tumors and Ewing's tumor contain no appreciable amount of intercellular reticulum. Melanoepithelioma contains an intermediate degree of reticulum. Hemangioendothelioma presents a picture in which the vessels are outlined, with reticulum penetrating to a varying degree into the cell masses, sometimes in great abundance. In this regard, endothelioma approaches sarcoma closely. Lymphosarcoma, leukemic adenosis, reticular cell sarcoma and Hodgkin's disease all present reticulum formation abundantly and indiscriminately, so that the presence of reticulum in this group will help to identify a tumor of mesenchymal origin but is of no help in subclassification. The study of any undifferentiated cellular neoplasm which is without obvious characteristics, whether located within the cranium or elsewhere in the body, is incomplete without preparation to show reticulum and collagen. The degree of abundance of reticulum varies among tumors of the same type and from field to field in the same section; the reticular pattern should therefore be employed as a histologic indication, although sometimes a strong one, among several in diagnosis rather than as a sole and conclusive criterion.

Much of the work on which this study is based was done in the laboratories of pathology of Western State Hospital, Fort Steilacoom, Wash., and the Clyde K. Emery Cancer Clinic, Los Angeles. The article was presented before the Indiana Association of Pathologists, Feb. 24, 1946.

ROLE OF STASIS IN THE DEVELOPMENT OF PULMONARY INFARCTS

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THE role of the veins of the legs as a source of pulmonary emboli has been repeatedly emphasized.[1] It has been demonstrated experimentally that stasis is necessary if red cell thrombi are to be produced consistently by the intravascular insertion of foreign bodies.[2] While the importance of stasis in the development of thrombi in peripheral blood vessels is generally known, the role of stasis in the genesis of pulmonary infarction is not widely recognized. This is true despite the fact that Zahn[3] in 1897 applied the clinical observation that pulmonary infarction is more likely to occur if embolization occurs in the presence of passive congestion (stasis) by binding the thorax of the experimental animal (rabbits) two days after emboli had lodged in the lungs. In 1912 Karsner and Ash[4] in a comprehensive review of the literature and experimental study demonstrated the importance of stasis in pulmonary infarction and stated

> . . . it can be seen clearly that simple embolism does not produce pulmonary infarction. . . . it may be safely said that not only is stasis a necessary corollary of the infarct, but also the greater the degree of stasis, the sooner is true infarction likely to appear.

The study reported here was undertaken to reinvestigate from the experimental standpoint the importance of stasis in the genesis of infarction following pulmonary embolism.

EXPERIMENTS AND RESULTS

Rabbits anesthetized by intravenous administration of pentobarbital sodium were used. A pulmonary embolus was produced by inserting into the jugular vein a 2 cm. length of wool knitting yarn which had been previously soaked in

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1. Homans, J.: New England J. Med. **211**:993, 1934. Rossle, R.: Virchows Arch. f. path. Anat. **300**:180, 1937. Neumann, R.: ibid. **301**:708, 1938. Hunter, E. C.; Sneeden, V. D.; Robertson, T. D., and Snyder, G. A. C.: Arch. Int. Med. **68**:1, 1941. Homans, J.: New England J. Med. **231**:51, 1944.
2. Moses, C.: Federation Proc. **4**:52, 1945; Proc. Soc. Exper. Biol. & Med. **59**:25, 1945.
3. Zahn, F. W.: Verhandl. d. Gesellsch. deutsch. Naturf. u. Aerzte **69**:9, 1897.
4. Karsner, H. T., and Ash, J. E.: J. M. Research **27**:205, 1912.

defibrinated dog's blood and thoroughly dried. The yarn inserted into the vein was gently pushed with a thin glass rod into the right side of the heart, and the opening in the vein was repaired with fine silk.

Controls.—Eleven rabbits in which this procedure was carried out were killed at intervals of from one to seven days thereafter. In 8 of these animals bland pulmonary emboli were found without evidence of circulatory disturbance in the lung. In 3 animals the embolus had failed to pass beyond the right side of the heart and was found there.

Compression of the Thorax.—Five rabbits were used for this experiment. After the blood-impregnated yarn had been pushed into the right side of the heart, the chest was firmly compressed with three wide synthetic rubber bands (½ by 3 in. [about 1 by 7.5 cm.]). In every one of these 5 animals hemorrhagic pulmonary infarction was evident in the lung containing the embolus within two to six days.

Ligation of Pulmonary Vein.—Ten rabbits sustained by intratracheal insufflation were used for this experiment. The thorax was opened, one of the pulmonary veins was ligated with linen thread, and the chest was quickly closed in an air-tight manner. None of these rabbits survived for more than sixteen hours, but hemorrhagic congestion involving the lobe drained by the ligated vein was evident in every animal within two to sixteen hours. Three of this group of animals were found at autopsy to have so-called "agonal thrombi" in the right side of the heart.

COMMENT

It is important to note that in all the experiments in which hemorrhagic pulmonary infarction was observed stasis and congestion were also present. In the rabbits without stasis bland embolism, without infarction, was noted. When, however, stasis and congestion were induced either by tying the pulmonary veins or by compressing the thorax, hemorrhagic infarction developed.

The tendency for "agonal thrombi" to develop in the right side of the heart was noted many years ago by Guthrie.[5] Boyd [6] commented on the frequency with which such thrombi are found in the right side of the heart of persons having pneumonia, which suggests the possible pathogenic role of stasis of the circulation in the right side of the heart in the presence of inflammatory pulmonary lesions.

From these observations it is evident that to prevent the development of pulmonary infarction, not only must stasis be prevented in the peripheral circulation to prevent the development of peripheral thrombi, but stasis and congestion in the pulmonary circuit must be avoided to prevent bland pulmonary embolism from yelding hemorrhagic infarcts. This does not mean that prevention of stasis in the pulmonary circulation can prevent fatal pulmonary embolism. Obviously, massive pulmonary embolism can mechanically prevent adequate oxygenation of the blood.

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5. Guthrie, C. C.: Blood Vessel Surgery, London, E. Arnold, 1912.

6. Boyd, W.: Pathology of Internal Diseases, Philadelphia, Lea & Febiger, 1944.

SUMMARY

Hemorrhagic pulmonary infarction could not be produced by the experimental method used in the absence of stasis and congestion in the pulmonary circulation. The observations emphasize the importance of preventing circulatory stasis not only in the systemic but also in the pulmonary circulation in order to prevent the development of hemorrhagic pulmonary infarcts.

Case Reports

INTESTINAL PERFORATION IN PARATYPHOID DUE TO SALMONELLA PARATYPHI B

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UP TO the present, approximately thirty cases of intestinal perforation in the course of paratyphoid have been cited.[1] In each of those cases the diagnosis of the type of Salmonella infection was based on the agglutination reactions of the patient's serum, on the biochemical and agglutinative properties of isolated organisms or on a combination of the two types of evidence; complete descriptions of bacteriologic investigations and analyses of antigenic structure were lacking. Because of the complete bacteriologic studies in the case to be reported, and the infrequency of pathologic reports of cases of this nature in American literature, it is thought worth while to publish our experiences.

REPORT OF A CASE

The following clinical information was obtained from the records of a prison hospital. Feb. 16, 1944, a German soldier was admitted to the prison hospital for further treatment of a gunshot wound of the left shoulder, incurred five weeks previously. The shoulder wound was granulating and uninfected. The patient had a slight fever. Two days later, headache, vomiting and diarrhea developed. Examination revealed an elevated temperature and tenderness, rigidity and a palpable mass in the right lower quadrant of the abdomen. The leukocyte count was 15,600. A laparotomy on the evening of the same day revealed a normal appendix, an edematous lower part of the ileum and about 200 cc. of clear, yellow fluid in the abdominal cavity; the appendix was removed, and, on subsequent examination, was not remarkable. From February 18, the day of the operation, to March 3, the day of death, the patient had a fluctuating temperature, reaching a maximum of 39.8 C. (103.6 F.) on the first postoperative day and a normal level in the last two days. Two leukocyte counts were 5500 and 6500 respectively. Agglutination tests, one week after the operation, were negative for Eberthella typhosa and Salmonella paratyphi A and B; at this time a blood culture was positive for S. paratyphi B. A urinalysis showed albumin, urobilinogen and a diazo reaction. The patient was dyspneic and cyanotic during the last eight days. A blood pressure reading was 105 systolic and 80 diastolic; the pulse rate fluctuated between 120 and 140. Death occurred suddenly March 3, 1944. The

1. (*a*) Bonamy, P.: Les perforations intestinales au cours des paratyphoïdes: Différentes methods chirurgicales de traitement, Thesis, Paris, 1932. (*b*) Grenier: Paratyphoïde B avec perforation intestinale, Progrès méd. **29**:114, 1913. (*c*) Hohenschild, M.: Ulcus ilei perforatum nach Paratyphus, Thesis, Munich, Lübeck, Gebr. Hohenschild, 1927. (*d*) Papin, F.: Perforations intestinales au cours de paratyphoïdes, Bull. et mém. Soc. nat. de chir. **56**:1342, 1930. (*e*) Pop, A.: Ein Fall von Perforationsperitonitis bei ambulatem Paratyphus B, Zentralbl. f. Chir. **56**:77, 1929.

patient was given plasma and 50 per cent dextrose intravenously; a total dose of 13.5 Gm. of sulfanilamide was given between February 17 and 21.

Autopsy (fourteen hours after death).—The body was that of a well developed but emaciated young adult man. The left shoulder revealed a shallow ulcer, 13 mm. in diameter, with a red, granular base. The pleural cavities were free of fluid and adhesions; the pericardial cavity contained about 40 cc. of clear, yellow fluid. A deep cervical lymph node, the size of an almond, revealed uniformly tan parenchyma on sectioning. About 300 cc. of thick yellow pus was in the abdominal cavity; the intestinal loops were coated irregularly by sheets of yellow fibrin and bound to each other by easily broken, fibrinous adhesions; the appendix was absent. The mesenteric lymph nodes were slightly enlarged, and, on section, presented uniformly pink parenchyma. The small intestine was distended, and parallel loops lay transversely in ladder pattern.

The esophagus, the stomach, the duodenum and the jejunum revealed no mucosal abnormalities. The mucosa of the lower third of the ileum displayed shallow ulcers on the antimesenteric side; the majority of the ulcers were oval, and their long axes were parallel to the long axis of the intestine. The bases of the ulcers varied; some were rough and brown with tan peripheries; others were streaked finely with gray and spotted with red. There were several widened, elongated and slightly depressed Peyer's patches, covered over with rugated mucosa. Two ulcers presented small perforations; one was 4 cm. and the other was 8 cm. from the ileocecal valve; the serosa around the perforations was covered with thick, easily removable yellow sheets of fibrin. The mucosa of the proximal half of the ascending colon presented small round superficial ulcers, averaging 5 mm. in diameter and less than 1 mm. in depth; their bases were smooth and tan, and their margins were occasionally elevated. The rest of the colon revealed no mucosal abnormalities.

The left lung weighed 352 Gm.; the right, 625 Gm.; there was uniformly diminished crepitance in all lobes; sections revealed deep red parenchyma oozing considerable serosanguinous fluid; the trachea and the bronchi contained foamy pink fluid. The heart weighed 280 Gm.; there were no abnormalities other than a flabby myocardium. The liver weighed 2,060 Gm., was increased in size and normal in shape; the capsule was flecked with strands of fibrin; the parenchyma was reddish brown finely mottled with tan. The spleen weighed 150 Gm. and was normal in size and shape; the capsule was partially covered with sheets of fibrin; the organ sectioned with ease, exposing reddish purple pulp, from which a moderate amount of diffluent material was removed on scraping. The gallbladder and the pancreas were not remarkable. The adrenal glands were larger and softer than normal; sections displayed light yellow cortex, accentuated vascular markings in the zona reticularis and gray medulla. Each kidney weighed 147 Gm.; the capsules were stripped with slight difficulty, rarely pulling away small pieces of cortex; the cortical surfaces were otherwise smooth; sections revealed grayish red parenchyma with accentuated cortical vascular striations; the pelves showed scattered mucosal petechiae. The ureters, the urinary bladder, the prostate and the testes were not remarkable. The brain weighed 1,358 Gm.; the only abnormalities revealed were accentuation of the vascular markings of the white matter throughout and a cyst, 3 mm. in diameter, in the midportion of the pituitary gland; the cyst contained gray, opaque, viscid material.

Microscopic Examination.—The pathologic diagnosis was: acute passive congestion of the lungs; atheroma of the aorta; focal necrosis and fatty degeneration of the liver; acute passive congestion of the spleen; subacute interstitial pancreatitis; parenchymatous degeneration, edema and focal necrosis of adrenal glands;

perforation of the ileum, hyperplasia and ulceration of Peyer's patches and paratyphoid fever; ulceration and colitis of the ascending colon, acute fibrinous peritonitis; focal necrosis and acute lymphadenitis of mesenteric and cervical lymph nodes; acute passive congestion and parenchymatous degeneration of the kidneys; cyst of Rathke's pouch, acute passive congestion of the brain.

In the lung, numerous alveolar spaces and bronchiolar lumens were filled with structureless eosinophilic granular material and scattered erythrocytes. There was dilatation of the capillaries of the pleura, the alveolar septums and the bronchiolar mucosa. Rare clumps of streptococci and plump rods were found in the alveolar spaces. There were no other abnormalities.

The heart was not remarkable. The aorta contained one focal intimal collection of lipoid cells. In the liver, several central and midzonal areas revealed loss of lobular structure; enmeshed in a fine fibrillar eosinophilic network were disjointed and shrunken parenchymal cells, erythrocytes and rare round cells and granulocytes. Elsewhere the basic lobular structure was preserved; the parenchymal cells revealed swelling, haziness of cell outline and occasionally numerous small intracytoplasmic vacuoles; the vacuolated cells had no particular lobular localization. The liver cords were often broken; the central veins and sinusoids were moderately dilated. Scattered Kupffer cells contained intracytoplasmic erythrocytes. The periportal spaces were not abnormal.

The capsule of the spleen contained scattered neutrophils. The trabeculae and the malpighian follicles were not remarkable. The venous sinuses of the red pulp were dilated; erythrocytes occupied the sinuses and the interstitium. Occasional endothelial cells contained intracytoplasmic erythrocytes. In one small area in the red pulp the sinus structure was almost completely obliterated by erythrocytes; enmeshed in the red cells were occasional endothelial cells, granulocytes and pyknotic nuclear debris, and at the periphery were numerous endothelial cells and scattered granulocytes.

In the adrenal gland, the cortical cells were separated from one another, and the capillaries were dilated. The cells of the zona fasciculata often lacked vacuolation, were swollen and had dense granular cytoplasm; scattered cells were enlarged and had almost completely vacuolated cytoplasm and hazy outline. Numerous cells of all zones were shrunken, with pyknotic or pale nuclei. A rare monocyte was present within the cords. In the zona fasciculata and reticularis there was one small focus of obliteration of cord pattern; the parenchymal cells were shrunken, vacuolated and pale, and their nuclei were pyknotic, fragmented, pale or absent; numerous round cells and neutrophils and eosinophilic granules were present in the focus.

Acinous cells of the pancreas occasionally revealed swelling and vacuolated pale cytoplasm. Acini and intralobular ducts were often distended with eosinophilic granular material; a rare neutrophil was enclosed. The intralobular and perilobular interstitium contained scattered round cells and rare granulocytes. A hemolymph node in the peripancreatic adipose tissue revealed in its sinuses numerous monocytes with intracytoplasmic erythrocytes.

Section near a site of perforation of the ileum revealed that centrally the structural pattern of all layers was completely replaced by structureless granular and fibrillar eosinophilic material with enmeshed nuclear debris and scattered clumps of bacteria. At the intact margins the mucosal pattern was largely obscured by numerous round cells, granulocytes, fine eosinophilic fibrils and coarse eosinophilic granules; small islands of lymphoid tissue were also present. The submucosal and muscular layers were infiltrated with round cells, chiefly monocytes; the submucosal vessels were dilated. The serosa was largely replaced by branching and anastomosing bands of fibrin with enmeshed neutrophils and nuclear debris.

Section through an enlarged Peyer's patch displayed hyperplasia of the lymphoid tissue of the mucosa; in some areas the lymphoid tissue was shallow and infiltrated with numerous monocytes; the glandular portion of the mucosa was largely absent over the lymphoid tissue, and revealed extensive postmortem degeneration elsewhere. The submucosa, and to a lesser extent the muscular layer, revealed numerous monocytes and scattered lymphocytes and granulocytes in the interstitium. The serosa was acutely inflamed as in the section through the area of perforation. The colon revealed focal absence of the mucosa and several small collections of round cells and granulocytes enmeshed in granular and fibrillar eosinophilic material at the base of the defect, in the submucosa.

The perinodal adipose tissue and capsules of mesenteric lymph nodes were focally infiltrated with monocytes, lymphocytes and occasional neutrophils. Sinuses were widened and filled with leukocytes, chiefly monocytes; the latter often contained intracytoplasmic vacuoles, nuclear debris or erythrocytes. Parenchymal capillaries were dilated, and scattered monocytes, plasma cells and granulocytes were in the interstitium. Germinal centers were absent. An arteriole was filled with fibrin and leukocytes. Both sinuses and parenchyma revealed scattered patches of granular and fibrillar eosinophilic material with round cells, nuclear debris, granulocytes and anucleate cells with pale pink cytoplasm. A cervical node revealed similar inflammatory changes to a lesser degree; in addition, the parenchyma contained discrete patches of dense fibrous tissue, in which were scattered extravascular clumps of erythrocytes, granulocytes, round cells and capillaries.

Glomerular loops and peritubular capillaries of the kidney were dilated; collecting tubules contained scattered hyaline and granular casts and crystals. The crystals were opaque, oval or round, and occasionally radially striated; some were irregular in shape. Cells of convoluted tubules were slightly swollen and hazy in outline; the lumens contained granular eosinophilic material. There was one small collection of lymphocytes and monocytes in the interstitium of the medulla. The pelvis was not remarkable.

Sections of cerebrum, cerebellum, pons and basal ganglions revealed similar changes. Meningeal and parenchymal capillaries were dilated. Rare Virchow-Robin spaces contained erythrocytes. Occasional neurons were shrunken, and their nuclei were pale. The glial tissue was not remarkable. The pars intermedia of the pituitary gland contained one large round space and numerous small round or irregular spaces lined by ciliated cuboidal epithelium and filled with structureless eosinophilic bars, granules and fine fibrils. The lining cells had granular eosinophilic cytoplasm and round or oval vesicular nuclei. Rare smaller spaces were lined by low cuboidal, nonciliated epithelium. The large space was surrounded by a thin band of dense fibrous tissue. The anterior and the posterior lobe of the pituitary gland were not abnormal.

At autopsy, samples were taken of heart blood, spinal fluid, Peyer's patch, spleen, mesenteric lymph node, peritoneal fluid, bile, urine and feces. The material was streaked directly on desoxycholate-citrate plates and placed in selenite F enrichment medium; the latter, after eighteen hours' incubation, was streaked on the plating medium. S. paratyphi B (Salmonella schottmülleri) was identified from all specimens, several colonies being picked from each plate. Typing of the culture was done by the method of Edwards and Bruner.[2] The

2. Edwards, P. R., and Bruner, D. W.: Serological Identification of Salmonella Cultures, Circular 54, Kentucky Agricultural Experiment Station, 1942.

antigenic formula was IV, V, XII,. . : b-l, 2. The identity of the organism was confirmed by Captain D. W. Bruner, Veterinary Corps, A. U. S. The biochemical reactions were typical. The organism produced hydrogen sulfide and utilized sodium citrate; it did not act on sodium *d*-tartrate, litmus milk or gelatin and did not form indole. Dextrose, rhamnose, xylose, dulcitol, mannitol and maltose were fermented, with production of acid and gas; lactose, sucrose and salicin were not fermented.

COMMENT

Among interesting findings at autopsy were two perforations of the ileum and a spleen of normal size and weight. Multiple perforations have been seen previously,[1a] and splenic size varies considerably,[1c] in paratyphoid. Pathogenic organisms were cultured from the spinal fluid, but the brain revealed no inflammatory response. A cervical lymph node displayed inflammatory changes similar to those seen in the mesenteric lymph nodes.

SUMMARY

In a case of perforation of the ileum in paratyphoid the outstanding clinical features were fever, headache, vomiting, diarrhea, abdominal pain, dyspnea and cyanosis. The early symptoms and signs suggested appendicitis and led to appendectomy. The major findings at necropsy were acute fibrinous peritonitis, two perforations of the ileum, hyperplasia and ulceration of Peyer's patches, ulceration of the ascending colon, acute lymphadenitis of mesenteric and cervical nodes and focal necrosis of lymph nodes, of the liver and of the adrenal glands S. paratyphi B (S. Schottmülleri) was isolated at autopsy from various organs and body fluids.

AN ACUTE FEBRILE ILLNESS CHARACTERIZED BY THROMBOPENIC PURPURA, HEMOLYTIC ANEMIA AND GENERALIZED PLATELET THROMBOSIS

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and

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THERE is a small but growing group of cases of an acute febrile illness characterized by marked and rapidly progressing anemia and thrombopenia. The first reported case was described by Moschcowitz[1] in 1925. Since then, to our knowledge, 7 additional cases have been reported.[2] These have all been similar clinically in that the patients had definite thrombopenia, rapidly progressing anemia and a febrile course terminating in death in from nine days to three weeks. In all the reported cases the patients have been females. Death has always been preceded by rather severe but nonlocalizing cerebral signs.

Pathologically, too, the reported cases have been similar in that petechial hemorrhages and platelet thrombi were present throughout the body.

We report here a case in which the clinical and pathologic aspects are similar to those described previously. Some new pathologic features are described, but nothing is added to the knowledge of the genesis of the disease. This is the first account of the appearance of this syndrome in a male.

REPORT OF A CASE

A 24 year old Italian baker was admitted to the Milford Hospital with rather severe vomiting of a few hours' duration. Two weeks previously he had had a severe cold with fever, prostration and cough but no sore throat. Convalescence was slow, and malaise continued. Three days before admission he felt generally ill and noticed hematuria. At that time laboratory studies revealed the following data: hemoglobin 11.5 Gm. per hundred cubic centimeters, red blood cells 3,500,000

From the Mallory Institute of Pathology, Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Milford Hospital, Milford, Mass.

1. Moschcowitz, E.: Arch. Int. Med. **36**:89, 1925.

2. (*a*) Baehr, G.; Klemperer, P., and Schifrin, A.: Tr. A. Am. Physicians **51**:43, 1936. (*b*) Friedberg, C. K., and Gross, L.: Arch. Int. Med. **58**:641, 1936. (*c*) Gitlow, S., and Goldmark, C.: Ann. Int. Med. **13**:1046, 1939. (*d*) Altschule, M. D.: New England J. Med. **227**:477, 1942. (*e*) Bernheim, A. I.: J. Mt. Sinai Hosp. **10**:287, 1943.

per cubic millimeter, white blood cells 8,700 per cubic millimeter. No platelets were seen in a stained film of peripheral blood. There were a few purpuric spots on the anterior abdominal wall. At 2 a. m. on the morning of admission he began to vomit.

His past history revealed no familial anemia or purpura of any type. There had been no exposure to or ingestion of any toxic drug, with particular reference to benzene, organic solvents in general, the sulfonamide compounds or fava beans.

In the hospital he was in a state of semiconsciousness, restless and uncooperative. His temperature was 101 F., and the blood pressure was 120 systolic and 70 diastolic. The pulse was rapid. He was pale and slightly jaundiced, with petechiae over the skin of the abdomen and that of the lower legs, in the mouth and in the conjunctivas. There were large petechiae and scratch marks on the face, over which there had been itching. The chest was clear with symmetric expansion. The heart was not enlarged, and no cardiac murmurs were heard. The abdomen was flat and not tender. There were a few palpable, nontender, freely movable small cervical lymph nodes, with no other superficial evidence of lymphadenopathy.

The laboratory data at this time were as follows: hemoglobin 36 per cent, hematocrit reading 18.5 per cent, red blood cells 2,180,000 per cubic millimeter, white blood cells 9,200 per cubic millimeter, icteric index 20. A differential count of the white blood cells revealed polymorphonuclear leukocytes 37 per cent, band forms 17 per cent, small lymphocytes 23 per cent, adult monocytes 17 per cent, eosinophils 4 per cent, basophils 2 per cent and blast forms 1 per cent. There were two nucleated red blood cells per hundred white blood cells. Reticulocytes composed 10 per cent of the red blood cells. The stained film of peripheral blood revealed moderate polychromatophilia of the red blood cells and marked thrombopenia. The osmotic fragility test gave the following data: hemolysis of 1 per cent of red blood cells in a saline solution with a concentration of sodium chloride of 0.51 per cent, 10 per cent hemolysis in 0.40 per cent saline solution, 50 per cent hemolysis in 0.33 per cent saline solution and 75 per cent hemolysis in 0.26 per cent saline solution. Cold agglutinins could not be demonstrated.

The patient remained comatose and became more jaundiced. Several transfusions of compatible blood failed to alter the progress of the illness. He became more irritable until his condition was that of restless stupor. He was entirely disoriented and unaware of his surroundings. On the third hospital day he died, approximately fifteen days after the onset of his present illness.

The clinical diagnosis was acute hemolytic anemia and acute thrombopenia, type and cause unknown.

Autopsy (six hours after death).—The body was that of a well developed and well nourished young white man, 175 cm. long and weighing approximately 145 pounds (65.5 Kg.). The skin was slightly icteric. Small petechiae were scattered over the body, the conjunctivas and the buccal membranes. The forehead bore many large petechiae and superficial lacerations consistent with scratch marks.

The smoothly lined abdominal cavity contained about 200 cc. of clear yellow-brown fluid. The peritoneal surfaces showed no petechiae. The pleural cavities were dry, showed no petechiae and were smooth except for an area of old fibrous adhesions at the right apex. Both the parietal and the visceral pericardium were covered by many petechiae.

The heart weighed 370 Gm., being slightly heavier than normal for the patient's size. The endocardial surface of the right auricle and ventricle, like the pericardium, contained many petechial hemorrhages. The endocardium of the left auricle and ventricle showed no petechiae.

The right lung weighed 580 Gm. and the left 630 Gm. The cut surface revealed many areas of hemorrhage, most marked in the lower lobes. The spleen was moderately enlarged and weighed 370 Gm. Except for its size it appeared grossly normal. The liver weighed 1,915 Gm., being moderately enlarged, with a smooth, yellow to brown mottled surface. The kidneys were congested and weighed 435 Gm. There were several small petechiae in the renal pelvis. The adrenal glands were of normal size and weighed a total of 17 Gm. Many hemorrhages, 1 to 2 mm. in diameter, were scattered along the periphery of the cortex. The vertebral and the sternal marrow were deep red. The marrow in the midfemoral region was yellow, with a thin layer of red marrow immediately subjacent to the bony cortex. The lymph nodes in the abdomen and the mediastinum were more prominent than usual, being 0.5 to 0.8 cm. in diameter. On section their cut surface was gray and wet. The brain weighed 1,420 Gm. The gyri were flattened, indicating moderate cerebral edema. There were no visible hemorrhages or areas of softening.

Bacteriologic Report.—On culture of the heart's blood no pathogenic organisms grew out. Both lungs contained moderate numbers of hemolytic Staphylococcus aureus.

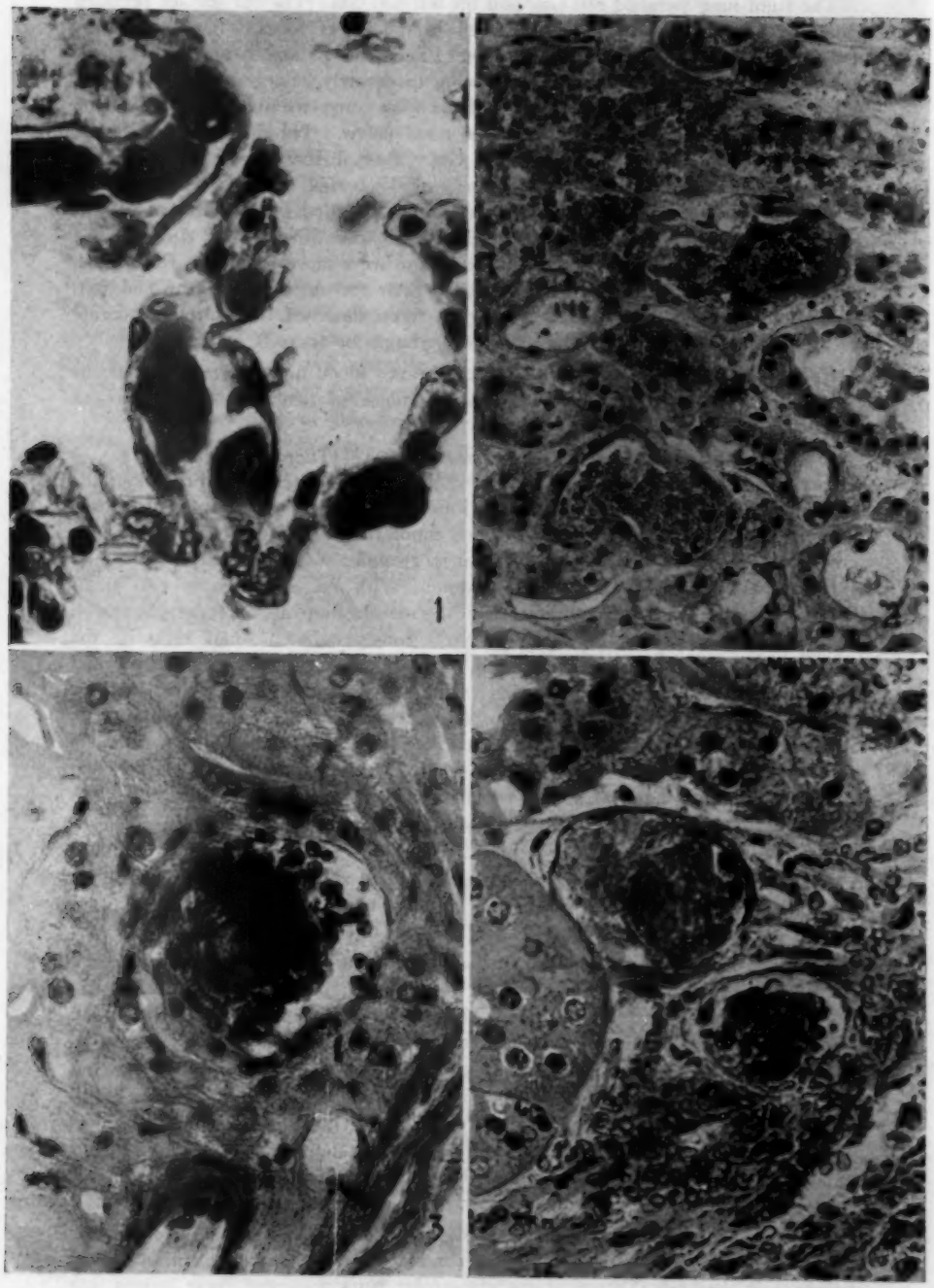
Microscopic Examination of the Organs.—Heart: There were many areas of hemorrhage throughout the myocardium of the right ventricle and throughout the left ventricle except for a subendocardial zone 2 mm. deep. In the areas of hemorrhage many occluded and partially occluded capillaries were found. The occlusions were produced by thrombi composed of finely granular material staining light pink with the phloxine and methylene blue stain. With the exception of two small thrombi along the walls of small arteries in the myocardium, all the lesions appeared in capillaries and larger, thin-walled vessels consistent with small veins or the transition vessels between capillaries and veins. Many capillaries with no thrombi showed definite swellings of endothelial cells. Mitotic figures were found in some of these endothelial cells. A few lesions showed some perivascular infiltration with large mononuclear leukocytes and occasional lymphocytes. A more complete description of these lesions will be given in a later section. Rare areas of myocardial necrosis were found associated with these thrombosed vessels.

Lungs: The lungs showed many small areas of hemorrhage and a few foci of bronchopneumonia. The capillaries contained only a rare, questionable thrombus. A great number of megakaryocytes were in the small vessels throughout both lungs (fig. 1). Some of these cells were so large that they extended into three adjacent microscopic sections, each section being 9 microns thick.

Spleen: The spleen was markedly congested. The malpighian corpuscles were well outlined, smaller than usual and inactive. No capillary thrombi were present, and a few megakaryocytes were seen. Occasional erythroblasts were present, but no significant amount of myeloid metaplasia was noted.

Liver: Many of the capillaries in the portal areas were thrombosed, but no such lesions were present in the sinusoids or large vessels. There was fatty metamorphosis of the hepatic parenchyma, and a few lymphocytes and an occasional polymorphonuclear leukocyte were found in the portal areas. The Kupffer cells contained a moderate amount of yellow-brown pigment and some phagocytosed red blood cells.

Kidneys: Many of the capillaries and small veins in the deeper layers of the cortex and in the medulla near the cortex contained thrombi similar to those present elsewhere in the body. Many of the glomerular tufts presented these lesions, but only rare thrombi could be found in the arterioles connected with the tuft. Several convoluted tubules were filled with fresh red blood cells, but no hemoglobin casts



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could be demonstrated. There was necrosis of some cells of the convoluted tubules, with regeneration, as evidenced by the presence of mitotic figures. Scattered tubular cells contained droplets characteristic of colloid droplet degeneration.

Adrenal Gland: Sections of adrenal gland showed marked lumen formation in the zona glomerulosa and zona fasciculata. Many hemorrhagic areas were present in the peripheral half of the cortex. The hemorrhages were in the lumens just mentioned and appeared to be recent and of the same age (fig. 2). Platelet thrombi of varied age were present in the capillaries and small arterioles and the veins of the zona glomerulosa. The endothelial cells lining these vessels showed definite swelling, proliferation and occasional mitotic figures. Migrating leukocytes were associated with many of the lesions. These leukocytes were found in the thrombi, at their periphery and lying free in the adjacent lumens (fig. 3). Small areas of necrosis were found in the periphery of the cortex.

Vertebral and Sternal Marrows: There was rather marked hyperactive erythropoiesis, which was predominantly at the erythroblastic level. Megakaryocytes appeared in the usual numbers, but the majority contained dark, pyknotic nuclei consistent with the appearance of old megakaryocytes. Many of the capillaries contained thrombi.

Brain: Sections of brain showed a few capillary thrombi with no hemorrhages.

Other Organs: Vascular lesions (thrombi) were also present in lymph nodes, the pancreas and the intestine.

Microscopic Examination of the Thrombi.—In order to substantiate the work of others and to determine as clearly as possible the nature of the capillary occlusions, several differential stains were used on tissues fixed in Zenker's solution or in solution of formaldehyde U. S. P. (1:10).

For routine examination tissues were stained with phloxine and methylene blue after fixation in Zenker's solution. Other stains [3] used were hematoxylin and eosin, Mallory's aniline blue connective tissue stain, Weigert's fibrin stain, phosphotungstic acid-hematoxylin, Giemsa stain (Wolbach's modification), Van Gieson and elastic tissue stains and iron stains. Sato's method was used for peroxidase granules.

Thrombi of varied appearance were found. We classified them as early, intermediate or old. We considered the earliest stage to be a thrombus composed of finely granular material which contained no red blood cells, fibrin, leukocytes, hyalin, collagen or bacteria. In some instances the early type of thrombi completely

3. Mallory, F. B.: Pathological Technique, Philadelphia, W. B. Saunders Company, 1938.

EXPLANATION OF FIGURE 1

Fig. 1.—Section of lung showing megakaryocytes filling capillaries. Phloxine and methylene blue; × 700.

Fig. 2.—Periphery of the cortex of an adrenal gland illustrating marked lumen formation and fresh bleeding into these lumens. Phloxine and methylene blue; × 260.

Fig. 3.—A vessel in the cortex of an adrenal gland with an old dense endothelized thrombus surrounded by monocytes and polymorphonuclear leukocytes. Van Gieson and elastic tissue stains; × 400.

Fig. 4.—Two vessels in the cortex of an adrenal gland illustrating the three stages of lesions described in the text. The larger vessel contains a thrombus of intermediate age overlaid with freshly precipitated platelets. The smaller one is partially filled by an old dense thrombus. Van Gieson and elastic tissue stains; × 400.

occluded the capillary lumen, while in others it was apparently deposited along one part of the wall. The accumulated granular material became more compact and fused to form the transition or intermediate type of thrombus (figs. 4 and 5). The third type was made up of a dense, homogeneous material closely adherent to the vascular wall, and in most instances was covered by endothelial cells. In our opinion thrombi of this type were old thrombi. Endothelial cells lining vascular channels had proliferated and covered the thrombi. Various combinations of these three types or stages were found. These combination forms were definitely laminated, and in some of them endothelial cells separated the different layers (figs. 4 and 6).

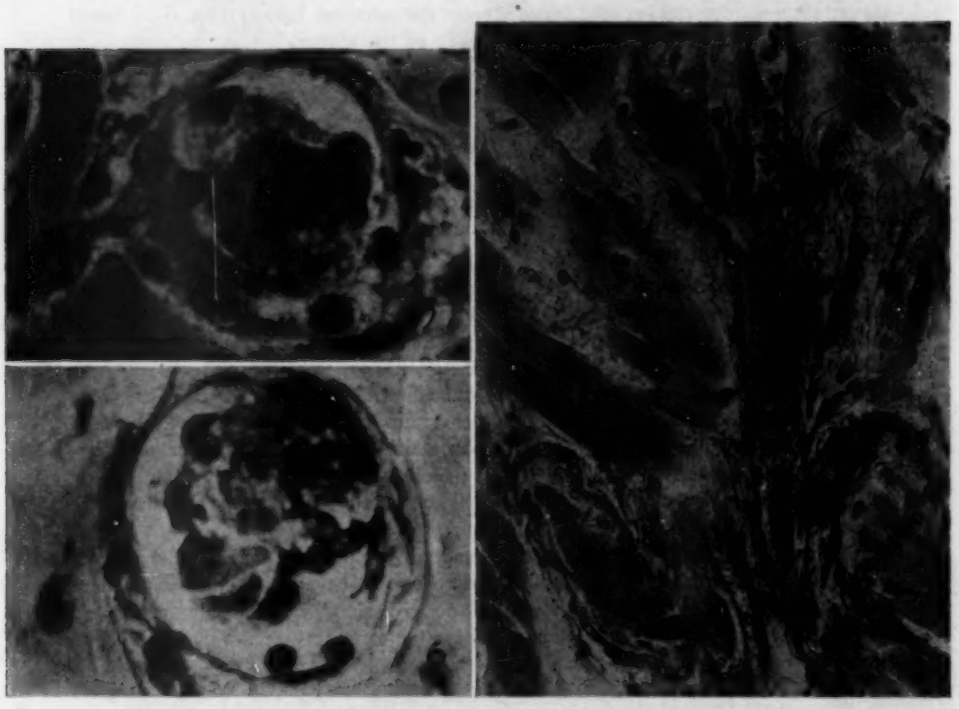


Fig. 5.—A small vessel with swollen endothelial cells contains a thrombus made up of early fused platelets and freshly precipitating platelets. Giemsa stain; × 725.

Fig. 6.—A laminated thrombus, covered by proliferated endothelial cells, almost completely occluding a small myocardial vessel. Giemsa stain; × 725.

Fig. 7.—The various stages of the developing platelet thrombi are demonstrated in this branching myocardial vessel. The lumen of the main channel, lined by swollen endothelial cells, is filled with the fresh granular material. The branches show older, dense thrombi. Van Gieson and elastic tissue stains; × 275.

Most of the lesions occurred in capillaries, some in small veins and a few in arterioles. A capillary was identified as a small, endothelium-lined lumen with no muscularis or elastic membrane. A venule or small vein was defined as a small, thin-walled vessel containing an occasional muscle fiber and having a very thin, incomplete elastic membrane. A small vessel with a well developed muscularis and a prominent elastic membrane was considered as an arteriole.

With the aniline blue stain, the finely granular substance was colored bluish pink, the old, homogeneous material a deep, dense red, and sometimes the intermediate, or early fused, layer took a deep blue. The Van Gieson method showed no pink-staining material consistent with collagen in any thrombus. The phosphotungstic acid–hematoxylin stain failed to demonstrate a fibrillar substance in any of the lesions. There was no fibrin and no iron-containing pigment. From their staining reactions and morphologic aspects these thrombi were considered to be made up primarily of platelets.

The lesions of dense material filled with nuclei resembled organized thrombi. However, stains for collagen failed to demonstrate its presence in any lesion. In a few of the lesions showing layers of different ages, the intermediate stage of the thrombus stained a homogeneous blue with the Mallory aniline blue method. The older, final stage never took this blue color, but always a deep red. No thrombus showed any suggestion of a pink stain with the Van Gieson method. In view of the aforementioned observations and the fact that the aniline blue stain may color many different materials a deep blue, we conclude that none of these lesions showed any organization or fibroblastic activity.

In the affected areas almost every capillary contained prominent endothelial cells with vesicular nuclei (fig. 7). These were present in uninvolved as well as in involved capillaries, but were more noticeable in the capillaries showing thrombi. The proliferation of, and mitotic figures in, these endothelial cells have already been mentioned. The migrating leukocytes in and around the lesions were peroxidase positive, consistent with monocytes.

COMMENT

From the findings we agree with Altschule [24] and with Baehr, Klemperer and Schifrin[28] and the others that these lesions are platelet thrombi deposited on vessel walls. Altschule suggested that the thrombi may have resulted from deposition of platelets on damaged endothelium. The swollen endothelial cells which we observed rather diffusely throughout the involved organs may represent the earliest histologic evidence of such endothelial damage. Following the deposition of the platelets, there is an increase in the density and compactness of the thrombus. Endothelial cells swell, proliferate and cover the platelet thrombus (fig. 6). On this endothelized surface more platelets can deposit and again become covered by endothelial cells. The process forms a lesion which contains nuclei and appears organized but in which there are neither fibroblasts nor collagen.

The clinical picture of this illness with its rapid febrile course, thrombopenia, severe anemia and death preceded by severe cerebral signs is characteristic of the other cases, previously described. The decreased erythrocyte count, the lowered hemoglobin level, the increased icteric index and clinical jaundice, the 10 per cent reticulocyte count, the moderate hemosiderosis of the spleen and the liver and the hyperplastic marrow satisfy our criteria for hemolytic anemia. The anemia developed to a marked degree prior to the appearance of the bleeding tendency. Histologically the small hemorrhages appeared to be quite recent, no hemolysis of red blood cells or deposition of iron-containing pigment being shown in these areas. These facts indicate that the jaundice was due to an intravascular hemolytic process and not to extravasation and breakdown of erythrocytes in the tissues.

We believe that the pathologic observations in this case do not suggest that the condition is in any way related to Werlhof's idiopathic disease known as purpura hemorrhagica, periarteritis nodosa, lupus erythematosus disseminata or other diseases of the erythema group. The histologic appearances are similar to those observed in animals in which the Shwartzman phenomenon had been produced.[4]

SUMMARY

A fatal febrile illness occurring in a young man was associated with rapidly developing hemolytic anemia and thrombopenia. Postmortem examination revealed many small hemorrhages and widespread platelet thrombosis of the small blood vessels. The type and the distribution of these vascular lesions are pathognomonic of illness of this type.

4. Shwartzman, G.; Klemperer, P., and Gerber, I. E.: J. A. M. A. **107**:1946, 1936.

EPIDERMOID CARCINOMA ARISING IN AN ENDOMETRIAL CYST OF THE OVARY

KENDRICK McCULLOUGH, M.D., and ESLEY R. FROATS, M.D., YONKERS, N. Y.
and
HENRY C. FALK, M.D., NEW YORK

PRIMARY epidermoid carcinoma of the ovary is rare. Its usual source is the stratified squamous epithelial lining of a cystic teratoma (dermoid cyst), which Ewing [1] mentioned. One of us (H. C. F.)[2] has encountered 3 cases in which the carcinoma was of that origin. In the present case it seems to have had another origin, the epithelial lining of an endometrial cyst of the Sampson [3] type. In this instance it is analogous to the epidermoid carcinoma of the uterine fundus but shows no mixture of adenomatous elements as in adenoacanthoma. It shows no evidence of teratomatous origin, no sebaceous glands, cartilage, nerve tissue or other teratoid element. The carcinoma appears confined to the wall of the cyst, though locally invasive. No evidence of metastasis is apparent.

To diagnose such a carcinomatous transformation of an ordinary ovarian cyst preoperatively is almost impossible. In the present case the carcinoma represents only an incidental finding in material routinely examined.

REPORT OF A CASE

An unmarried white woman, 61 years old, was admitted to St. Johns Riverside Hospital, Yonkers, N. Y., July 13, 1944, complaining that her abdomen had slowly and steadily increased in size for the past five years and that there had been increasing constipation for one and one-half years and lately pain in the abdomen. Her father died of cancer at 65 years; the mother, of an accident.

Her health was always good. Ten years before, she had hives lasting ten days, the result of ingestion of seafood. Six years before, she had a growth on the right side of the upper lip, which was treated by roentgen ray, with no recurrence or visible metastasis. Menstruation ceased eight years before, with no bleeding since. For six days she had noted pain in the right upper abdominal quadrant, rather severe, and slight shortness of breath in the miderect position. A mass could be felt in the lower part of the abdomen, apparently ovarian and cystic, large and without tenderness. Her general appearance indicated good nourishment. The pupils were equal and reacted to light and distance. There

From the Surgical Service and Laboratory, St. John's Riverside Hospital, Yonkers, N. Y.

1. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 679.
2. Falk, H. C.: Personal communication to the authors.
3. Sampson, J. A.: Arch. Surg. 3:245, 1921.

was an old scar on the right side of the upper lip. The cervical nodes were not enlarged. The thyroid gland was not enlarged. No dyspnea was noted; the breath sounds were clear, with no pulmonary dulness; there was slight impairment of respiratory excursion. The heart sounds were of good quality, without

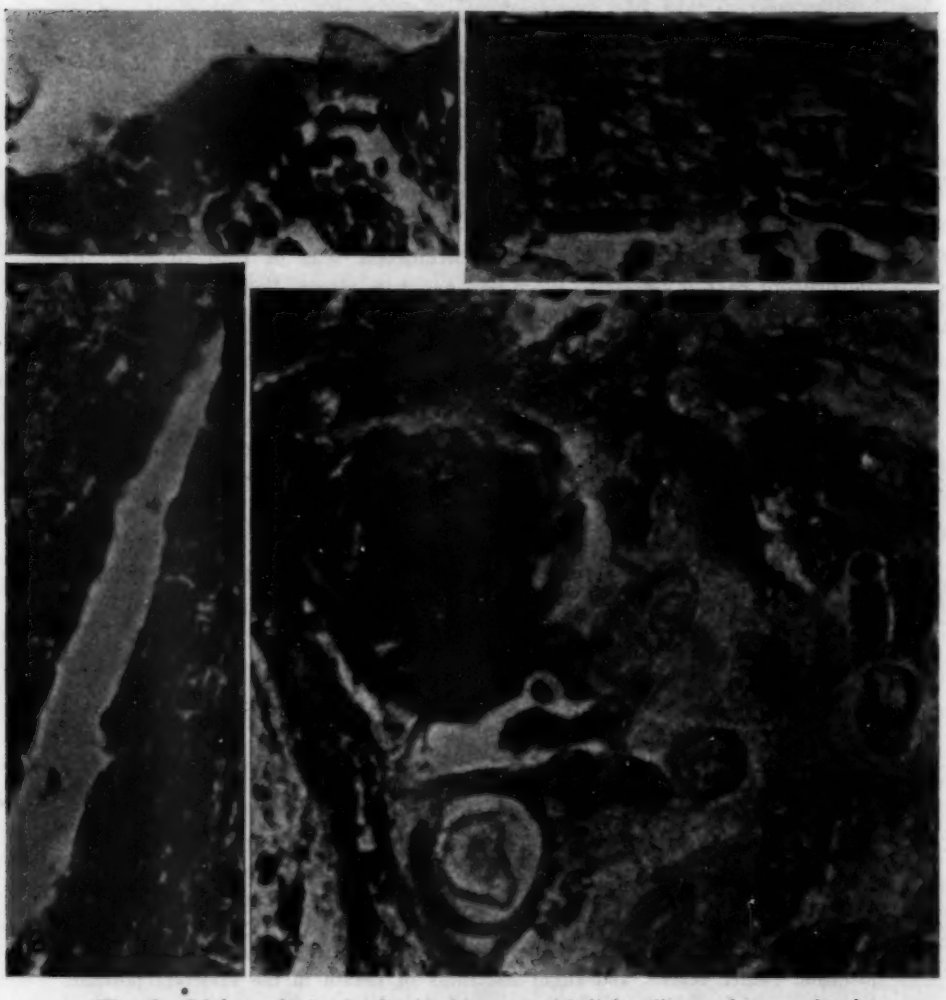


Fig. 1.—Lining of simple, low columnar epithelial cells at the mouth of a wide crypt. Lymphoid stroma is seen on one side. × 608.5.

Fig. 2.—Narrow tubular gland. × 608.5.

Fig. 3.—Lining of transitional epithelium with flattened surface cells. × 608.5.

Fig. 4.—Epidermoid carcinoma showing one mitotic figure and two keratotic whorls. × 608.5.

murmurs; there was no apparent hypertrophy. The abdomen showed no evidence of free fluid. The liver was not palpable. The extremities showed no tremor and no edema; the reflexes were normal. The blood pressure was 148 systolic and 80 diastolic.

The blood count on admission showed hemoglobin 10.7 Gm. per hundred cubic centimeters, erythrocytes 4,620,000 per cubic millimeter, color index 0.86 and leukocytes 13,300 per cubic millimeter; the differential count was basophils 1 per cent, eosinophils 4 per cent, staff neutrophils 5 per cent, segmented neutrophils 63 per cent and lymphocytes 22 per cent. There were no red cells of abnormal morphologic aspect. The urine varied in specific gravity from 1.006 to 1.016 and showed no albumin, sugar or acetone, few leukocytes and no blood or casts. The total protein of the blood was 6.83 Gm. per hundred cubic centimeters, the serum albumin 3.9 Gm. and the globulin 2.9 Gm.; the albumin-globulin ratio was 1.34. The blood type was Landsteiner O, Rh negative.

Operation, July 15, 1944, revealed a large cyst of the right ovary, unilocular, containing an estimated 4,000 cc. of thick, clear, dark brown fluid. The pedicle was attached to the right infundibulopelvic ligament, and there was a band of tissue adhering to the posterior peritoneal wall. The cyst and the attached right fallopian tube were removed.

The cyst showed a tough wall with many slight rough elevations of its lining, which otherwise was smooth. Histologic examination showed occasional areas which resembled endometrium, with few shallow glandular crypts, some dilated, lined by low columnar epithelial cells, which covered some of the nearby surface. Beneath this epithelium, small areas resembling endometrial stroma occurred, with densely packed small stellate cells and a few groups of large histiocytes. The thickened areas of the lining showed stratified squamous epithelium in apparent neoplasia. There were loss of polarity of the squamous cells, variation in size and shape, keratotic whorls, variation in size and pigmentation of nuclei and many mitotic figures. Bordering the thick epithelial masses were thinner sheets of stratified epithelium of the squamous and transitional types, sometimes undermining the columnar epithelium adjacent, showing loss of polarity of the cells. The wall of the cyst was formed of dense fibrous tissue, invaded by many small groups and masses of the neoplastic squamous cells. Considerable inflammatory reaction was present, especially about areas of tumor.

The postoperative course was uneventful for a short time. After three months, constipation and pain in the abdomen returned, followed by urinary frequency, pus and blood in the urine. Examination revealed a mass the size of a lemon in the left broad ligament. The patient was hospitalized in another institution, and death followed signs of uremia, Jan. 12, 1945. Permission for an autopsy was not obtained.

To determine whether vitamin A deficiency was related in any way to the changes in the lining of the cyst, a record of the diet was obtained for the week after discharge. This was representative of the diet followed for many years. It showed no deficiency, yielding about 8,000 U. S. P. units of the vitamin daily, occasionally over 10,000. This bears out the finding that the squamous metaplasia of vitamin A deficiency occurs in non-neoplastic epithelium only, while epidermoid carcinoma commonly occurs in regions where epithelium other than stratified squamous is found, such as the bronchus, the urinary tract or the endometrium, in persons who show no evidence of this deficiency.

SUMMARY

Epidermoid carcinoma was observed arising in the epithelium of an endometrial cyst of an ovary.

Obituaries

JOSEPH McFARLAND, M.D.

1868-1945

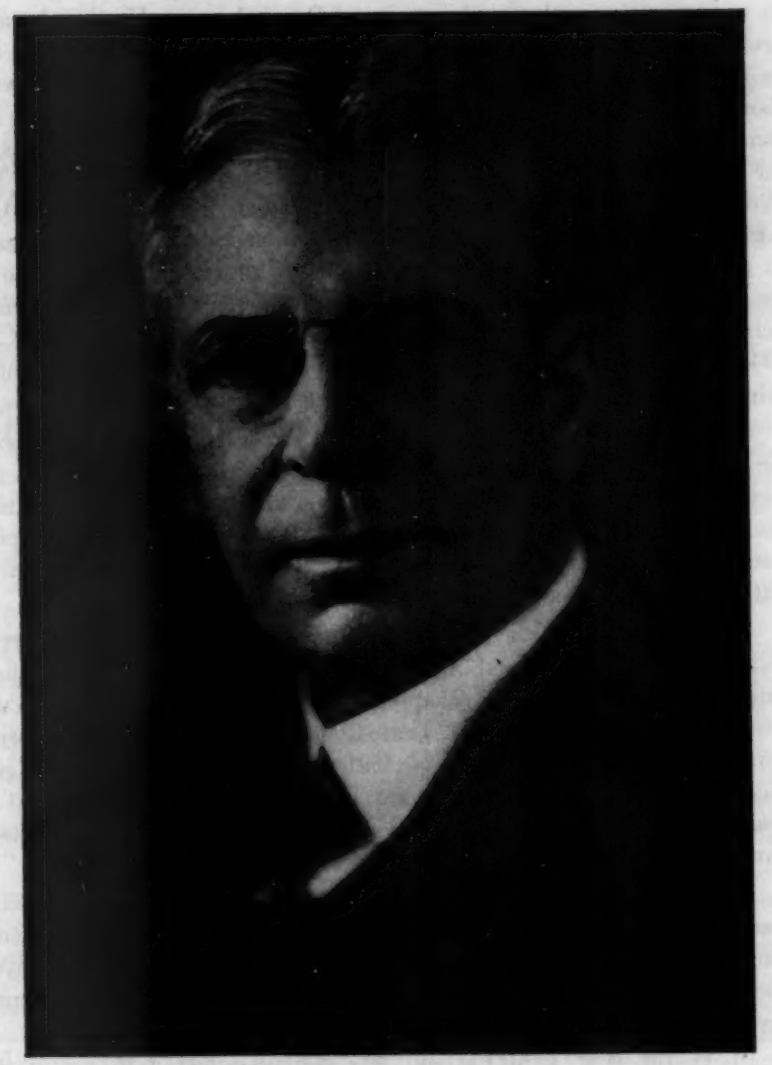
Joseph McFarland was born in Philadelphia, Feb. 9, 1868, several months after the death of his father, who succumbed to pulmonary tuberculosis. He early became interested in science. With his mother, he frequently visited museums of natural history. When 15 years old he lectured at the Lauderbach Academy, now extinct, on the story of a pebble.

McFarland graduated from the medical school of the University of Pennsylvania in 1889. An inspiring teacher was William Osler, who advised him to spend ten years studying pathology as an introduction to medicine. In pursuance of this, the young man went to Heidelberg, Germany, where he studied under Julius Arnold and worked in bacteriology under Paul Ernst. Later he went to Vienna, Austria, and took morbid anatomy under Kolisko and neuropathology under Oberheimer. Several years later he made the acquaintance of Rudolph Virchow and worked for a time in Fränkel's laboratory at Halle, Germany.

His first appointment was at the University of Pennsylvania, that of assistant to the professor of pathology under John Guiteras at a salary of $50 a year. Six months later he was made demonstrator in pathology at $1,000 a year. On this income he married Virginia Kinsey in 1892, and he "lived with her for fifty years without a single quarrel."

In 1894 he took on the professorship of pathology in the Philadelphia Polyclinic Hospital and College for Graduates in Medicine, holding it for two years without salary and without a single student. He then resigned to accept the lectureship on bacteriology, the first at the University of Pennsylvania, and began to prepare for his first book, "The Pathogenic Bacteria." He was at this time and for the next six years director of the new laboratory for biologic products opened by the H. K. Mulford Company, who began the manufacture of antidiphtheritic serum. When the laboratory outgrew its quarters and moved to Glenolden, Pa., and a full time director became imperative, he withdrew. Almost immediately Parke, Davis & Company offered him the post of consultant, which he held for ten years and resigned to become a full time professor.

This account is based on information given by Dr. Helen McF. Woodbridge, Dr. McFarland's daughter, and on his autobiographic sketch.



Joseph McFarland

For the next twenty years, McFarland held the chair of professor of bacteriology and pathology in the Medico-Chirurgical College, until its amalgamation with the University of Pennsylvania. He then became professor of pathology with Allen J. Smith, when "began . . . the most happy period of my institutional life, for Smith and I were thoroughly congenial and our association perfectly harmonious." He lectured on general pathology in the veterinary and dental schools of the university, holding also the rank of professor of pathology in the Woman's Medical College of Pennsylvania, where he succeeded A. O. J. Kelly and was followed by Fred D. Weidman when forced to resign to give full time to the university. On his retirement for age, he at once became professor of pathology in the Temple University Dental School, a post which he held at the time of his sudden death, Sept. 22, 1945. He was pathologist to several hospitals and served the Philadelphia General Hospital (Blockley) as such for more than thirty years.

He was a member of the College of Physicians of Philadelphia, the American Medical Association (secretary and chairman of the section on Pathology and Bacteriology), the American Association of Pathologists and Bacteriologists (a founder), the Philadelphia Pathological Society (president), the American Society of Clinical Pathologists (honorary member) and other associations.

Dr. McFarland was a versatile scholar and prolific writer. He read easily German, French and Spanish. He published some 200 medical papers, contributed special chapters to systems and textbooks, and wrote the following books: "Text Book upon Pathogenic Bacteria" (nine editions), "Text Book of Pathology," "Biology—General and Medical," "The Breast" (with John B. Deaver), "Fighting Foes Too Small to Be Seen" and "Surgical Pathology." He made important contributions to the study of tumors of the salivary glands.

He was the minister for several years in a struggling church, preached frequently in the summer places to which he went, and made many commencement addresses. He was an excellent lecturer, enjoyed a keen sense of humor, and was a friendly and helpful guide to young physicians.

In World War I McFarland was commissioned a major in the Medical Corps of the United States Army in April 1917 and served as chief of the laboratory services at various hospitals in this country. He acquired pulmonary tuberculosis in the latter part of 1919, was given hospital treatment, and was discharged in February 1920.

In 1942 the Philadelphia Medical Society conferred the Strittmater Award on McFarland as being the outstanding medical man in Philadelphia in 1941.

I. DAVIDSOHN.

Notes and News

Appointments, Etc.—Lieutenant Colonel G. Howard Gowen has been appointed chief of the division of cancer control in the Illinois Department of Public Health.

Elmer L. Sevringhaus, professor of medicine at the University of Wisconsin, has accepted an appointment as director of clinical research for Hoffmann-La Roche, Inc.

Harry Goldblatt has resigned as professor of experimental pathology and associate director of the institute of pathology at Western Reserve University School of Medicine, Cleveland, effective in August, to become director of an institute for medical research at Cedars of Lebanon Hospital, Los Angeles.

Grant for Study of Tropical Diseases.—The Marcelle Fleischmann Foundation has made a grant of $20,000 a year for a ten-year period to the department of public health and preventive medicine of Cornell University Medical College for the study of tropical diseases. The specified purpose of the gift is to promote the study of immunologic and allergic manifestations of exotic diseases and to provide for a better understanding of their prevention and treatment in relation to other allergic diseases. The investigations at Cornell will be under the direction of Morton C. Kahn.

Award.—The American Foundation for Tropical Medicine has made the third award of the Richard Pearson Strong Medal for outstanding achievement in the field of tropical medicine to Brigadier General George R. Callender, United States Army, director of the Army Medical School.

American Board of Pathology.—This board will hold examinations in San Francisco, July 1 and 2, if there are a sufficient number of applicants. Pathologists interested should submit their applications at once to Dr. F. W. Hartman, secretary, Henry Ford Hospital, Detroit 2, Mich.

The Army Institute of Pathology.—The Meritorious Service Plaque was awarded on Feb. 7, 1946 to the Army Institute of Pathology. The letter of transmittal from the Surgeon General to the director of the institute, Colonel J. E. Ash, reads in part as follows: "Under the provisions of Circular 345, War Department 1944, as amended by Section 1, Circular 331, 1945, I take great pleasure in awarding the Meritorious Service Plaque to the Army Institute of Pathology, your command, for superior performance of an exceptionally difficult mission and for untiring devotion to duty of the personnel of this unit during the period July 1945 to 31 December 1945."

Books Received

A. A. A. S. Research Conference on Cancer: A Conference of Papers and Discussions Presented at the Summer Meeting of the Section on Chemistry of the American Association for the Advancement of Science at Gibson Island, Maryland, July 31–August 4, 1944. Publication Committee: Dean Burk, chairman; Ralph G. Meader, John J. Bittner and Vincent du Vigneaud. Edited by Forest Ray Moulton. Pp. 333, illustrated. Washington, D. C.: American Association for the Advancement of Science, 1945.

This volume represents well the status in 1944 of research on certain fundamental problems of cancer. There are five sections with well prepared papers and pertinent discussions on: the virus approach to the etiology of cancer, carcinogenesis, enzymes, diet, experimental chemotherapy. The conference and the report are of great credit to the American Association for the Advancement of Science as well as to the participants. The understanding of cancer has been advanced.

Preventive Medicine and Public Health. By Wilson G. Smillie, M.D., D.P.H., Sc.D. (hon.), professor of public health and preventive medicine at Cornell University Medical College, New York. Price $60. Pp. 607. New York: The Macmillan Company, 1946.

The special feature of this book is its point of view that the teaching of preventive medicine, that is the protection and the promotion of personal and family health, should be done as an essential part of the teaching of clinical medicine. "The content of the text brings out the fact that teaching of preventive medicine will be most effective if it is integrated with the teaching of clinical medicine. Thus the members of the departmental staff in preventive medicine should have clinical appointments, and should teach their subjects, not from a textbook, but at the bedside, in the clinic, and in the home." The book is a highly important contribution to advance the teaching of preventive medicine.

Journal of the History of Medicine and Allied Sciences. Volume 1, number 1, January 1946. Pp. 183. Price $7.50 a year in the United States, Canada and Latin America; $7.80 elsewhere. Published quarterly. New York: Henry Schuman, 1946.

This quarterly will have no rival in this country except the *Bulletin of the History of Medicine,* edited by H. E. Sigerist, which largely reflects the work of the Baltimore school. Competition, however, is disavowed; George Rosen, the editor of the new journal, says: "it will not compete with, but will supplement the *Bulletin.*" Associated with Rosen to constitute the board of editors, are Erwin R. Ackerknecht, Max H. Fisch, John F. Fulton and Josiah C. Trent. The international scope of the publication is shown by an impressive list of 43 consulting editors of North and South America and many countries in Europe. The format is pleasing. In the 183 pages of this first number are eleven scholarly articles that are well worth reading. A "Notes and Queries" section under the charge of Max H. Fisch may well prove to be one of the most attractive features of the magazine. All who are interested in medical history will wish the new journal a full measure of success.

Protozoology. By Richard R. Kudo, D.Sc., professor of zoology at the University of Illinois, Urbana. Third edition. Pp. 778, with 336 illustrations. Price $8. Springfield, Ill.: Charles C Thomas, Publisher, 1946.

Tables of Representative Values of Foods Commonly Used in Tropical Countries. By B. S. Platt. Medical Research Council, Special Report Series, no. 253. Pp. 41. Price 25 cents. London: His Majesty's Stationery Office, 1945.

Bovine Trichomoniasis. By Banner Bill Morgan, Ph.D., parasitologist and assistant professor of veterinary science, University of Wisconsin, Madison. Pp. 150, illustrated. Price, $3.25. Minneapolis, Minn.: Burgess Publishing Company, 1945.

Bovine trichomoniasis is a venereal disease and an important cause of abortion and sterility in cows. It is curious that from 1897 to 1925 Brucella abortus was regarded as the only cause of infectious bovine abortion. It seems as if somehow Trichomonas foetus, easily seen under low magnification, was overlooked in smears of exudate examined under high power. Bovine trichomoniasis has been found to be widely distributed and to cause serious losses in animal husbandry. Prevention requires that infected bulls be not used for breeding. Morgan's monograph is a comprehensive summary of the literature on the disease, to the knowledge of which he himself has made significant contributions. The bibliography contains 408 items, almost all published since 1925. The description of T. foetus is complete in all respects. In other parts the monograph is more a rather rambling catalogue of facts than a compact, closely organized composition. The arrangement into chapters is rather loose. The last chapter, headed "Miscellaneous," contains statements that should have been incorporated into other chapters. There is no index. But there can be no question about the value of the monograph as a reliable source of information of all kinds about bovine trichomoniasis.

Book Reviews

A Study of Endometriosis, Endosalpingiosis, Endocervicosis, and Peritoneo-ovarian Sclerosis. A Clinical and Pathologic Study. By James Robert Goodall, M.D., formerly professor of clinical gynecology and obstetrics at McGill University. Second Edition. Pp. 151, with 19 illustrations. Price $5.50. Philadelphia: J. B. Lippincott Company, 1944.

In the preface the author states that in his further research he "has found only corroborative evidence to substantiate the facts and opinions expressed in the first edition." The only major change appears to be the adding of a section on endometriosis of the urinary system (pages 77 to 88) to the chapter on extrauterine endometriosis. Criticisms, factual and otherwise, in reviews of the first edition remain unnoticed. The book is an elaborate and repetitious exposition of the author's observations and ideas on endometriosis, but there is no thorough review and analysis of the literature on this topic. The first chapters deal briefly with matters of historical, classificational and nomenclatural interest. Uterine endometriosis is divided into intrauterine and parietal, each composed of glands and stroma, that is "mixed," or of stroma only. The relation of the intrauterine or "endometrial endometriosis" to endometrial hyperplasia as currently understood is not clearly defined. Then come more detailed chapters on uterine endometriosis, the stromal form of which, it is claimed, does not respond in any way to the cyclic influences that affect the endometrial glands. The forms and the sites of extrauterine endometriosis are described in chapter 11. The rest of the book takes up the causation, the clinical manifestations and the treatment of endometriosis and its effects, also allied conditions, e. g., peritoneal and ovarian sclerosis. The original illustrations are inadequate. There is no cleancut, convincing illustration of stromal endometriosis. Its relations to fibroma, myoma and sarcoma, though much discussed, remain vague. While the book contains much instructive information about forms, locations and results of endometriosis, the frequently repeated explanations of its growth are speculative. It is not known, as claimed on page 13, that the action of estrogen is limited to the outer two thirds of the endometrium. It is not conclusively settled that endometriosis originates

only in the endometrium. That endometriosis is an expression of "vitiated endocrine function" or of excess in estrogen production is not definitely known. In the paragraphs on "endocervicosis" also assumption takes the upper hand. The following dogmatic statement (page 15) appears to overlook reports of cases of endometriosis in pregnancy: "Were all the endometrial cells susceptible to the menstrual hormones, the destructiveness of endometriosis would be increased tremendously, or were it possible for active endometriosis and pregnancy to co-exist, the destructiveness of endometriosis would be inconceivably increased, owing to the great surcease of the ovarian hormones during pregnancy. Fortunately for womankind active endometriosis and pregnancy *never* co-exist." (The italics occur in the original.)